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Stereotactic radiosurgery: an update

David Hailey

May 2002

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Interim Report

Stereotactic radiosurgery: an update

David Hailey

May 2002

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This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion, and attempts to be current to the date of publication. Comments received following circulation of the draft have been considered in preparation of the current version which has been issued as an interim report, pending further external review.

Additional information and comments relative to the paper are welcome, and should be sent to:

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The literature search for this report was undertaken by Ms. Leigh-Ann Topfer, Canadian Coordinating Office for Health Technology Assessment (CCOHTA)

SUMMARY

- This report has been prepared in response to a request from Alberta Health and Wellness for an update on advice provided in earlier assessments by the Foundation on stereotactic radiosurgery (SRS) treatment.
- The present report is consistent with findings from assessments by other agencies that the quality of the available evidence on SRS effectiveness in comparison with other types of treatment is limited.
- There is still no evidence that any one form of SRS is superior over another. There is some indication, from small studies, of similar outcomes from the Gamma Knife (GK) and focused linear acceleration (LINAC) versions of SRS.
- There is increasing use of fractionated stereotactic radiotherapy (FSRT) as an alternative or supplement to SRS. There is some indication, from small series, that FSRT may have advantages over SRS in some situations in terms of incidence of complications.
- A version of SRS, using robotic technology (the Cyberknife), that enables treatment in any part of the body is now commercially available and preliminary clinical results have been published.
- The GK approach is more expensive than that using standard LINAC approaches or FSRT. Costs of using recent developments in LINAC technology are not yet clear. The need remains to go beyond cost analysis to economic evaluation, taking appropriate account of local circumstances.
- Many journal articles, as well as HTA reports, confirm advice given in earlier AHFMR assessments that excellent quality assurance and placement of SRS in specialized centres are essential.
- On the basis of information available in the published literature, conclusions on the place of SRS in the applications considered in the assessment are as follows:
  - ***Acoustic neuroma*:** Microsurgery remains the treatment of choice for many patients. SRS has a useful place where surgery would have an unacceptable risk or be refused. Long term follow up data on SRS treatment are still comparatively limited. FSRT appears to have potential as an alternative to LINAC or GK SRS.
  - ***AVMs:*** Microsurgery and SRS should be regarded as complementary approaches. Surgery is preferred if the lesion can be safely excised. Further information is emerging on longer term complications of SRS.
  - ***Trigeminal neuralgia:*** There are a number of options for treatment of trigeminal neuralgia and the place of SRS in its management does not seem to be established.

- ***Brain metastases*:** SRS has a place in the management of appropriately selected patients, is a useful option when the patient is not a candidate for surgery and may offer advantages through relief of neurological symptoms. SRS plus radiotherapy appears more effective than radiotherapy alone.
- ***Brain tumours*:** SRS appears to be a useful adjunctive treatment, though with reletively limited success with malignant glioma, in appropriately selected patients. It is helpful where surgery is not possible or carries unacceptably high risks.
- ***Parkinson's disease:*** Encouraging results have been reported by one centre, but the place of SRS in the treatment of Parkinson's Disease does not appear to be established.
- ***Epilepsy*:** The efficacy of SRS in the management of epilepsy appears not to have been established, other than in association with its use in treatment for AVMs or brain tumours.

- SRS is now being used in Alberta, with a LINAC facility at the Tom Baker Cancer Centre, Calgary for treatment of malignant disease.
- Any referral of patients from Alberta for SRS treatment outside the province should be to centres of excellence with experience in management of the condition in question, and take account of the availability of other, appropriate, treatment options.

Abbreviations and Acronyms Used in the Report

AOVM: Angiographically occult vascular malformation

AVM: Arteriovenous malformation

FDA: US Food and Drug Administration

FFP: Freedom from progression

FSRT: Fractionated stereotactic radiotherapy

GBM: Glioblastoma multiforme

GK: Gamma Knife

GOS: Glasgow Outcome Scale

Gy: Gray

KPS: Karnofsky Performance Status

LINAC: linear accelerator – based radiosurgery

LYS: Life years saved

MRI: magnetic resonance imaging

MS: multiple sclerosis

NF2: Neurofibromatosis Type 2

NSCLC: Non small cell lung cancer

PRL: Prolactin

QALY: Quality adjusted life year

QOL: quality of life

RCT: Randomised controlled trial

RF: Radiofrequency

RPA: Recursive partitioning analysis

RTOG: Radiation Therapy Oncology Group

SCLC: Small cell lung cancer

SRS: Stereotactic radiosurgery

SS: Statistically significant

TGN: trigeminal neuralgia/ neuropathy

UPDRS: Unified Parkinson's Disease Rating Scale

WBRT: Whole brain radiotherapy

XRT: External beam radiotherapy

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INTRODUCTION

This report has been prepared in response to a request from Alberta Health and Wellness for updated advice on the use of stereotactic radiosurgery (SRS) treatment.

The request was in the context of referral of persons for SRS treatment at centres outside the province. In 1998, AHFMR undertook an assessment of SRS, a form of radiotherapy which uses a focused, conformal radiation dose to treat lesions in the brain [1]. There was interest at the time in regard to referral of patients outside the province for SRS treatment, which was not available in Alberta.

The Foundation also prepared a separate assessment of treatment options for acoustic neuroma, considering both SRS and microsurgery [2]. Separate brief reports have been prepared on application of SRS to metastatic melanoma [3] and on a new type of SRS device, the CyberKnife [4]. The present request from the ministry arose because of continuing questions regarding appropriate options for referral of patients for SRS and other treatments, and need for advice on any significant technical developments.

The 1998 AHFMR report noted that there had been several previous reports on SRS by health technology assessment agencies. The Foundation's assessment confirmed findings from these other assessments that:

- the quality of the available evidence on the effectiveness SRS was limited;
- there was insufficient information to determine the comparative effectiveness of the two most common approaches approaches, the Gamma Knife (GK) which uses cobalt – 60 sources to provide radiation, and the focused linear accelerator (LINAC) which uses a modified version of standard radiotherapy equipment.
- data on comparison of SRS with other types of treatment were also limited;
- the GK approach was more expensive than that using the LINAC;
- excellent quality assurance and placement of SRS in specialized centres were essential.

The potential SRS caseload for Alberta was uncertain, but might be 30 to 50 per year. Treatment using an Alberta-based LINAC SRS facility might cost about $4,000 per case, at a caseload of 30 per year, compared to $8,000 to $11,000 for LINAC SRS treatment in Ontario and approximately $30,000 with GK SRS in the U.S.A.

The AHMR assessment on treatment options for acoustic neuroma [2] noted that microsurgery was the primary treatment option and that there was evidence, from methodologically weak studies, that SRS was efficacious in treatment of this type of tumour in suitably selected patients. There was limited evidence on the comparative effectiveness of these two approaches, both of which had short and long term complications.

The approach taken for the present assessment has been to consider the recent literature that has emerged since completion of the two previous AHFMR HTA reports. All applications of SRS are considered, with an emphasis on clinical outcomes. No detailed consideration has been given either to technical details of SRS equipment or approaches to its operation. Neither has there been a detailed appraisal of the quality of the studies that have been located, though comment related to methodological issues is made on some studies. The methodology used for the assessment is outlined in Appendix A.

TECHNICAL ISSUES

No detailed appraisal or description of technical issues related to SRS has been undertaken for this assessment. The following brief details on a number of matters related to equipment and different technology that have emerged since the previous reports are presented as further points for consideration in taking decisions on use of radiosurgery services for Albertans.

Stereotactic radiotherapy

On reviewing the literature for this assessment, it was apparent that a number of reports had emerged on the use of fractionated stereotactic radiotherapy (FSRT). The 1999 AHFMR report [2] concluded that fractionated radiation through the LINAC approach might have an advantage over standard approaches to SRS but that good evidence of benefit from fractionation in treatment of acoustic neuroma had yet to emerge.

Data on FSRT in comparison with SRS and microsurgery/XRT are still limited, but from the studies reviewed for this assessment there do appear to be some indications of comparative benefit. FSRT will need to be considered as an alternative option to SRS. A 1999 Canadian commentary [5] indicated that experience with this approach suggested that it would find a role in intracranial treatment, and some details on its application to treatment of brain tumours are given by Becker et al. [6].

Kondziolka et al. [7], in discussion of treatment of SRS for meningioma, make the point that although FSRT confines radiation more than conventional fractionated radiotherapy, it is not a conformal irradiation approach. The volume of the brain that is irradiated exceeds that irradiated in SRS, though the consequent effect may be lessened by the number of fractions. Presumably, this distinction will become less clear as newer types of LINAC devices, which offer conformal planning and delivery of radiation, become more widely available.

Intensity – modulated radiation therapy (IMRT), which uses non- uniform radiation beams to achieve conformal dose distribution, is a further emerging option [8, 9]. Benedict et al. [10] describe analysis of four cases involving small brain lesions where an intensity-modulated stereotactic radiosurgery approach was used to model treatment planning. They conclude that IMSRS demonstrated significant dosimetric improvements for small, irregularly shaped lesions of the brain when compared to treatments using multiple static fields or standard SRS arc techniques with circular collimators.

Developments with LINAC technology

In an article presenting an exchange of views between users of LINAC and GK versions of SRS, Bova [11] draws attention to the advent of multi leaf collimators for high resolution intensity-modulated planning, extra-cranial approaches, fractionated stereotactic radiotherapy systems and high dose rate LINACS.

A further SRS system that is now commercially available is the CyberKnife, a LINAC-based device that makes use of robotic manipulation to position the accelerator. This is a significant addition to the range of options for SRS, as the device can be used to treat lesions anywhere in the body, rather than only in the head. The CyberKnife was approved by the FDA in August 2001 for radiosurgery for lesions anywhere in the body where radiation treatment is indicated. Chang et al. provided preliminary results on the use of the system in treating 72 patients with malignant intracranial tumours [12]. A report by Inoue et al. [13] refers to use of the CyberKnife in Japan between 1998 and 2000 for treatment of 136 sites (67 of which were brain metastases) in 94 patients.

Developments with cobalt 60 – based systems

The Model C Gamma Knife was introduced in 1999 and includes an automated patient positioning system, an option to use this to establish the coordinates for each iso centre and an integrated helmet changer. This may reduce total time required to complete treatments [14].

A rotating SRS device known as the rotating gamma system has been developed in China. This uses 30 cobalt – 60 sources in a revolving hemispheric shell that is aligned with a coaxial shell with groups of collimator holes that can be selected to produce different beam diameters [14].

Reliability of SRS approaches

In the exchange of views between Bova and Goetsch [11], reference is made to use of the GK at the San Diego centre over its first 62 months during which there were two days of planned downtime and no cancellation of treatments because of machine unavailability. A reload of cobalt – 60 sources in 2001 required clinical downtime of 21 days; Goetsch comments that for newer models of the GK, reloading would take only 10 – 15 days. In comparison, the LINAC system at the University of Florida had treated more than 1,700 patients over a 13 year period with a back up LINAC being needed in only two patients.

Both types of SRS can be expected to have high mechanical reliability.

Proton radiosurgery

SRS using protons offers advantages over other types SRS through improved energy distribution of the delivered dose and greater ability to irradiate deep structures. The technology remains expensive and relatively few centres have used this approach in routine health care. A review of the technology by Harsh et al. [15] refers to experience at the Massachusetts General Hospital using the STAR apparatus for proton radiosurgery. Between 1991 and 1998 there were 416 patient treatments and early results for AVMs, acoustic neuromas and brain metastases are said to be comparable to those produced with other stereotactic techniques.

Recent HTA Reports

Table 1 gives brief details of some HTA reports that have been published since the AHFMR report. In general, the pattern of findings is much the same as in earlier HTA report. Quality of available evidence is regarded as poor, and there is no good evidence to support one form of SRS over another. The call by the ANAES report for work to establish the population need for SRS, appropriate organisational arrangements and comparative effectiveness seems particularly apposite. Included for comparison is a summary of an early HTA on this technology, which provides an illustration of the persistence of some of the unresolved issues.

Table 1: Some recent health technology assessments of stereotactic radiosurgery

Organisation)	Conclusions
CEDIT [16] (France) May 1997	• Studies available do not provide evidence demonstrating the superiority of either the Gamma Knife or the LINAC procedure in terms of clinical benefit to the patient. • Technological progress and cost of investment favour the LINAC but quality assurance procedures are more complex. Relative simplicity of use and sturdiness favour the Gamma Knife, but high purchase price, cost of replacing the cobalt source…and restriction to use for treating brain lesions militate against it. • Overall, the Committee does not see any decisive argument in favour of purchasing a Gamma Knife • CEDIT recommends that a unit, dedicated to stereotaxic radiotherapy, which will be able to treat all patients in the Ile-de-France, be set up.
ANAES [17] (France) May 2000	• The data do not allow evaluation of comparative efficacy of SRS and other options or of the GK and LINAC. • Cost studies can be used only as a guide and contribute little to whether there is any potential economic advantage in favour of one method or another. Nevertheless, cost information suggests opting for a GK or a dedicated LINAC if number of treatments is high and for a modified LINAC if the number is lower. • Number of centres dedicated to brain SRS needs to be reconsidered (France had 17 modified LINAC sites and 1 that used the GK). Centres should be dedicated and there should be a study of actual SRS requirements for the population • Further research should be encouraged to provide prospective comparison of efficacy and safety of the GK and dedicated LINAC • New emerging indications for SRS should be assessed prospectively and validated before wider use. This should also apply to other stereotactic radiation procedures, such as FSRT.

Table 1: Some recent health technology assessments of stereotactic radiosurgery (cont'd)

Organisation)	Conclusions
Medicare Services Advisory Committee [18] (Australia) October 2000 Recommendation accepted by Minister August 2001	• Poor quality of published data precludes definitive assessment of safety and efficacy of the GK • Not possible to determine whether SRS is superior to treatment with conventional methods • Insufficient information to determine whether one method of SRS is superior to another • Not possible to perform a true economic evaluation of GK SRS or comparators in managing patients with AVMs, brain metastases or acoustic neuroma • Cost estimates suggest that cost per treatment with GK is 1.7 to 2.9 times more expensive than LINAC over a range of possible scenarios • Overall, microsurgery remains an acceptable intervention, particularly for patients with small, easily accessible AVMs and acoustic neuromas • SRS may be effective treatment for selected groups of patients, eg those with surgically inaccessible lesions • Recommended that additional public funding for the GK not be supported.
Swedish Council on Technology Assessment in Health Care [19] January 2002	• AcSwedish report indicates successful treatment of AVMs with a GK ranges from 60-84%, with best results on small AVMs. • Reported obliteration frequency somewhat less for SRS using protons or LINAC, explained by the fact that these are applied to a higher percentage of larger AVMs which are more difficult to treat. • Rate of serious complications with permanent neurological loss is about 4%. • There is poor scientific documentation of relative benefits and risks of SRS treatment of AVMs and no scientific documentation on cost-effectiveness of the method.

Table 1: Some recent health technology assessments of stereotactic radiosurgery (cont'd)

Organisation)	Conclusions
Veterans' Affairs Technology Assessment Program [20] 1997 (USA)	SRS is relatively safe and effective for treating brain metastases in selected patients, and seemed to offer greater survival than XRT, but lack of data from high quality studies preclude any definitive assessment of its effectiveness relative to standard treatment. Randomised trials are needed to properly address the research questions
Wessex Institute [21] October 2001 (UK)	(considered SRS for brain tumours and AVMs) • Poor quality evidence for the effects of radiosurgery • Results from different studies were extremely difficult to compare • Studies to date cannot reliably predict magnitude of any potential benefit or how effects might compare to microsurgery
Australian Institute of Health [22] February 1990	• Cost/effectiveness advantage over invasive surgery for some patients with AVMs or benign tumours • LINAC has potential to meet/exceed the GK capabilities Issues: • Proven record of the Gamma Knife • Greater flexibility, lower cost of LINAC • Need for assurance on the reproducibility, effectiveness and safety of LINAC • Continuing rapid development of focused LINAC methods • Availability of commercial systems (implies regulatory agency approval for devices) • Availability of existing expertise using focused radiation • Capacity of existing radiotherapy services

Studies Related to the Efficacy or Effectiveness of SRS

In this section, overviews are given, by disease or condition, of studies that included outcomes data that might help to determine the efficacy or effectiveness of radiosurgery. As reported in other assessments, the overall quality of evidence is limited through methodologically weak study designs and inconsistent or incomplete reporting of data.

Acoustic neuroma

The 1998 AHFMR report [1] considered six studies of SRS in treatment of acoustic neuroma. These gave indications of benefit through local control and acceptable longer-term outcomes, but there were some concerns regarding possible complications. SRS appeared to be a useful option for appropriately selected patients, but surgery would often be the preferred option. A further paper suggested observation is a reasonable management strategy in carefully selected patients with acoustic neuroma, but diligent follow-up is required to assess if active treatment is required.

Treatment of acoustic neuroma was considered in more detail by the 1999 AHFMR report [2] which assessed a further 15 papers dealing with SRS in this application and also ten papers reporting studies of microsurgical techniques. The report concluded that there was evidence, from methodologically weak studies, that SRS is efficacious in the treatment of acoustic neuroma in suitably selected individuals. However, evidence on the comparative effectiveness of SRS and microsurgery remained limited and both had associated short and long term complications. There was no evidence of any difference in effectiveness between the LINAC and GK approaches in this application.

Studies located in the present assessment are listed in Table 2. Eleven of these used FSRT, one of these being a comparison with GK, there were 17 other GK studies and five that used LINAC. There were three cohort studies, the rest being case series.

The cohort study comparing GK with FSRT indicated that these approaches gave similar rates of tumour control but that patients treated with FSRT had higher rates of serviceable hearing preservation. This indication of possible superiority of FSRT is qualified by the small numbers in the study and the relatively short follow up. In the second cohort study, surgery or SRS (GK) appeared to give better outcomes than observation. Comparison of the two interventions was less clear; it was suggested that both were effective for small and medium tumours. The third cohort study indicated superiority of FSRT over observation.

Table 2: Studies on SRS treatment of acoustic neuroma

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Andrews et al, 2001 [23] Cohort study 10/94 – 8/00	N=122 with acoustic neuroma Philadelphia, USA	FSRT, n=56 GK, n=69 N=1 GK + FSRT	Mean follow up 119 wk SRS, 115 wk FSRT For patients with follow up >6 mo, actuarial control rates 98% SRS (n=63), 97% FSRT (n=46) Comparable low cranial nerve morbidities for each group. Audiometric follow up mean 82 wk FSRT (n=34), 68 SRS (n=17). Probability of maintaining same Gardner – Robertson grade SS higher in FSRT group	Suggest SRS (GK in this case) and FSRT are comparable treatments for acoustic neuromas, higher rates of serviceable hearing preservation suggests FSRT may be preferable to alternative treatments.
Bertalanffy et al., 2001 [24] Consecutive case series 8/92 – 10/95	N= 40 with acoustic neuroma Vienna, Austria	GK 20 SRS only, 21 previous surgery, 1-4 times	9 patients lost to follow up, 32 observed for at least 36 months. Tumour decreased or stable in 29, increased in 3. For 9/14 with useful hearing – improved in 2, stable in 4, deteriorated in 3. Tinnitus improved in 6/13, deteriorated in 2. Vertigo increased in 6/23, stable in 8, decreased in 9.	Patients discharged within 24h of treatment. High drop out rate.
Brophy, 2000 [25] Case series 7/89 – 6/94 for surgery, unclear for SRS	a) N=37 with tumours <3cm b) n= 59, characteristics not specified Adelaide, Australia	a) LINAC b) Microsurgery	a) no patient required surgery; for 14 with >2y follow up, 64% showed decrease in tumour size. 2 patients developed hydrocephalus b) 70% had good facial nerve function	Only limited results and clinical details presented
Flickinger et al., 2001 [26] Case series 8/92 – 8/97	N=190 previously untreated unilateral tumours Pittsburgh, USA	GK	Median follow up 30 mo (max 85); >1y MRI in 147, >2y clinical exam in 159. N=3 resection after SRS. Tumour increases observed in further 10 Actuarial freedom from resection 97.1%, image results 91% Tumour shrinkage in 35% of 147 at >1y TGN developed in 4 cases, facial neuropathy in 2 Hearing preservation: preserved for 77% of 133 assessable patients; serviceable hearing in 81% of 75, testable speech discrimination in 90% of 137	Authors note higher rates of tumour growth control and hearing preservation compared with their series prior to 1992, also 'minimal risk' of TGN or facial neuropathy. Technical changes included improved planning, use of MRI.

Table 2: Studies on SRS treatment of acoustic neuroma (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Fukuoka et al., 1997 [27] Case series 1991 -1995	N= 43 with unilateral acoustic neurinoma, mean 4 mL diameter (0.1 – 18.7) Sapporo, Japan	GK	Mean follow up 36 mo (22-55) Actuarial hearing preservation 83% at 1y, 77% 2 and 3 y,	
Fuss et al., 2000 [28] Case series, retrospective evaluation 11/89 – 9/99	N= 42 of 51 with acoustic neuroma with follow up of at least 12 mo. Mean volume 16.0 mL (2.2 – 32.4) Heidelberg, Germany	FSRT	Mean follow up 42 mo (17-131) Actuarial tumour control 100% at 2y, 95% at 5y after treatment. Actuarial useful hearing preservation 85% at 2 and 5y (n=27, 6 had further impairment but retained useful hearing, 4 had new hearing loss.) Actuarial normal facial nerve function preservation 100% at 5y	Authors report treatment policy of SRS or FSRT for small tumours, FSRT for older patients, larger tumours and those with tumour at only hearing ear.
Kagei et al., 1999 [29] Case series 3/91 – 2/96	N=39 with acoustic neuroma Sapporo, Japan	FSRT; most common schedule 44Gy in 22 fractions, 5.5 weeks Stereotactic boost in n=33	Median follow up 24mo(6-69) Tumours decreased in33%, unchanged 64%, increased 3%. 2y actuarial control 97% Actuarial preservation of testable hearing 96% at 2y (n=25), of initial hearing class 79% and 60% at 1 and 2y No permanent facial or TGN, actuarial rates of radiation – induced TGN 16% at 1,2y; for facial neuropathy 8%	Separate results from different treatment protocols used not clear.
Kalapurakal et al., 1999 [30] Case series 1992 -1997	N=19 with acoustic neuromas at high risk for SRS -induced cranial neuropathy Philadelphia, USA.	FSRT, 36 Gy in n=6; 30 Gy in n=13, 6 weekly fractions.	Median follow up 54 mo (34 –65) Tumour shrinkage n=10, stable n=9. N=15 evaluable trigeminal nerve function, n= 16 evaluable facial nerve function. None developed transient or permanent trigeminal or facial neuropathy	Suggest FSRT may offer a superior therapeutic ratio to SRS in the management of large acoustic neuromas, as evidenced by absence of post-treatment neuropathy.

Table 2: Studies on SRS treatment of acoustic neuroma (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Kida et al., 2000 [31] Case series	N=20 with NF2 and bilateral acoustic neuroma Komaki City, Japan	GK 70% prior surgery	Mean follow up 33.6 mo (18-24) Treated tumours: 15% decreased, 35% minor response, 50% no change. Untreated: 60% no change, 40% progressed. Of n=12 treated who had hearing at SRS, hearing in treated ear worsened in 8, was stable in 3, improved in 1. Contralateral hearing in n=13 worsened in 7, was stable in 6.	A commentary on the paper draws attention to frequent need for surgery for other types of tumour in such cases
Kwon et al., 1999 [32] Case series 5/90 – 2/98	N=77 with follow up >6mo from 101 with acoustic neuroma Seoul, S Korea	GK	Mean follow up 55mo (7-90) Tumour control rate 91%, size reduced in 53%	
Lederman et al., 1997 [33] Case series 11/93 – 7/96	N=38 with 39 acoustic neuroma New York, USA	LINAC. FSRT, 20Gy in 4 or 5 weekly fractions	Median clinical follow up 27.1 mo, imaging follow up 16.3 mo N=23 with <3cm tumour: 61% decreased, 39% stable. N=21 9% hearing improved, 86% stable, 5% worse N=16 with > 3cm tumour 81% decreased, 19% stable. N=11 18% improved hearing, 73% stable, 9% worse No new permanent neuropathies	
Liščák et al., 1999 [34] Case series 1992 - 1996	N= 121 with acoustic neuroma Prague, Czech Republic	GK; primary treatment in n=97	Median follow up 24mo (2-48) 6 deaths, 2 hydrocephalus, 4 unrelated 4/23 with useful hearing prior to SRS impaired to grade III. 3/98 with no useful hearing attained this after SRS. Decrease in tumour volume in 41.3%, increase in 4.1%	

Table 2: Studies on SRS treatment of acoustic neuroma (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Meijer et al., 2000 [35] Prospective consecutive case series 1992 – 1998	N=37 with acoustic neuroma Amsterdam, The Nertherlands	FSRT N=35 first treatment, 2 followed previous surgery 20Gy in 5 fractions for dentate patients, n=25, single high dose fraction for edentate individuals	Mean follow up 25 mo (12 –61) 5y actuarial control rate 91%, TG nerve preservation 97% n=23 with useful hearing had actuarial preservation rate of 66% at 5y (17 treated with fractionated schedule)	
Møller et al., 2000 [36] Cohort study 1998 -1997	N=211 with acoustic neuroma Bergen, Norway	Surgery, n=100 GK, 40Gy to centre n=69, (42 of 111 lost to follow up) Observation, n=35	For surgery, House-Brackmann scale 1-2 for 25/25 small or intrameatal tumours; 22/33 medium, 19/29 large, 7/13 giant. Facial function reduced after GK in 8/68, 4 HB 2 or 3. In small and medium size tumour cases having surgery, 5/12 preserved hearing; hearing preserved in 80% GK In GK series, tumour growth in n=4 In observation series 54% of neuromas showed growth, 80% lost hearing.	Limited details of results, difficult to adequately compare different modalities Authors conclude GK or surgery effective for small and medium size, surgery for large and most medium size
Niranjan et al., 1999 [37] Case series 8/87 – 12/97	N=29 Unilateral intracanicular tumours Pittsburgh, USA	GK, 13 Gy for patients with hearing, >= 14Gy if no hearing	Follow up median 33mo (9 – 106) 10/11 maintained hearing, 4/5 who received >14 Gy deteriorated 6/29 had decreased tumour volume, 20 unchanged, 3 enlarged but then stabilised. None developed TGN	Do not fully distinguish between the outcomes from the different protocols used.
Norén, 1998 [38] Review of treatments at two centres, 6/69 – 10/94	N=669 with acoustic neuroma Stockholm, Sweden and Providence, USA	GK	Long term growth control in 95% unilateral tumours up to 3 mm diameter Early facial weakness, numbness declined from >30% in 1970s to 2% in 1990s Preservation of hearing 65-70% in more recent cases Hydrocephalus induced by tumour in 9.2%	Varied diagnostic procedures, associated surgical technique, patient characteristics etc over this long period

Table 2: Studies on SRS treatment of acoustic neuroma (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Petit et al., 2001 [39] Case series 12/93 – 1/2000	N=47 with acoustic neuroma Baltimore, USA	GK; using lower dose approach, median marginal tumour doses 12 Gy following surgery and 12 Gy where SRS as primary treatment.	Median follow up 3.6y (1-7) 5y actuarial control rate 96% (progression in 2 patients, no others up to 3.7y) For n=23 at 3.5 – 7y 52% had decreased, 4% remained stable. 4/32 with residual hearing at SRS had diminished response, actuarial 5y hearing preservation rate 87%	Authors indicate lower complication rates than for other series.
Poen et al., 1999 [40] Case series 4/94 – 1/98	N= 33 with acoustic neuroma (10 NF2) Stanford, USA	LINAC, FSRS; 3 fractions of 7Gy over 24h	Median follow up 2y (0.5 –4) for n=31 (2 unrelated deaths) Tumour regression in 34%, stable in 63%, progressed in 3%. Actuarial freedom from tumour progression at 2y 93% 5 trigeminal nerve injury (2 with TGN prior to SRS), 1 facial nerve injury Preservation of useful hearing 77% of n=63	
Prasad et al., 2000 [41] Case series 3/89 – 3/99	N= 153 with acoustic neuroma Charlottesville, USA	GK; primary treatment in 96, prior surgery in 57	Mean follow up 4.3y (1 –10) Tumour size: SRS only reduction in 81%, no change 13%, increase 6%;SRS +microsurgery 65%, 25%, 10% Of n=48 with residual hearing pre SRS, was improvement in 6%, no change in 58%, deterioration in 35%. Patients' subjective assessment indicated 63% had worsening of haring	
Regis and Pellet, 1998 [42] Consecutive case series 7/92 –8/97	N=100 from total of 400 with acoustic neuroma Marseille, France	GK	At 3y follow up: Hearing: 70% with normal hearing maintained useful hearing; 50% who had useful hearing had some hearing. N=7 had CSF shunting. Other functional side effects resolved within 2y except for one case with impaired trigeminal function	Comparison made with microsurgical series of n=224 between 6/83 and 12/90 which had higher complication rates and 1.75% mortality, but also appeared to have had a larger proportion of cases with higher grade tumours

Table 2: Studies on SRS treatment of acoustic neuroma (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Roche et al., 2000 [43] Case series 7/92 – 12/97	N=27 with NF2 and 35 acoustic neuromas. Marseille, France	GK 12 prior surgery	Mean follow up 32 mo (6-70) 74% tumour control at last follow up. 1 persistent post SRS facial nerve deficit. Class 1 and 2 hearing preserved in 57% of 12 who had these levels pre SRS	
Roos et al., 2000 [44] Case series 1997 - 2001	N=23 with acoustic neuroma, including 3 NF2 Adelaide, Australia	LINAC	Median follow up 32 mo (12-51) for n=18 11 reduction in tumour size, 6 no change Of n=13 with pre SRS hearing, 5 unchanged, 8 deteriorated (median 34 mo)	Part of review of early experience
Sakamoto et al., 2001 [45] Case series 1992 - 1999	N=21 of 72 with acoustic neuroma Sapporo, Japan	FSRT; 36-50Gy in 20-25 fractions	Actuarial cumulative decrease in tumour size 38% at 2y, 80% at 3y Annual rates of hearing loss in 2nd and 3rd years after SRS SS slower than rate before irradiation.	Considers the group of patients who had their hearing levels examined > 3mo before treatment. Hearing loss usually permanent; rate of hearing loss decreased after SRS.
Shirato et al., 1999 [46] Cohort study 1989 - 1997	N= 77 with acoustic neuroma Sapporo, Japan	FSRT, n=50, 44 Gy, later reduced to 36-40 Gy in 22 fractions Observation only, n=27	Mean follow up 24.1 mo FSRT, 37.8 mo observation. 4y actuarial control rates 86.2% FSRT, 24.0% observation No permanent neuropathies in FSRT group Actuarial 3 and 5y class preservation rates for observation group 60.9%, 31 %; 3 and 5y both 53% for FSRT (not SS)	NSD in tumour size, between two groups
Shirato et al., 2000 [47] Case series, comparison of tumour types 1991 -1999	N= 65 with acoustic neuroma, 20 with cystic and 45 with solid tumours. Obihiro, Japan	FSRT, 36 –50Gy in 20 – 25 fractions	Mean follow up 37 mo (6-97) Actuarial 3y rates of no enlargement 75% for solid tumours,55% for cystic (SS). Actuarial reduction rates 31% and 93% 3y preservation rates for hearing 50% and 76% for solid and cystic tumours	

Table 2: Studies on SRS treatment of acoustic neuroma (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Song and Williams, 1999 [48] Case series 7/95 – 6/98	N= 30 with 31 acoustic neuromas Baltimore, USA	LINAC FSRS, 25Gy in 5 daily fractions	Minimum follow up 6mo (6-44) 29% tumours decreased, 71% same size Of n=12 with useful hearing, 9 retained after SRS . Of n=25 having hearing prior to SRS, 2 improved, 10 unchanged, 13 worsened Subjectively, n=3 had improved balance, 665 unchanged, 24% worse N=2 developed new TGN, I persisted, n=2 had improvement of pre SRS trigeminal symptoms	Initial short term study
Spiegelman et al., 2001 [49] Case series 1993 - 1997	N= 44 with acoustic neuroma Tel Hashomer, Israel	LINAC	Mean follow up 32 mo(12-60) Volume reduction in 75% of 44 tumours, 98% controlled 9/13 with preserved hearing prior to SRS maintained serviceable hearing and one improved (hearing preservation rate 71%) Actuarial facial neuropathy rate 8%	
Subach et al., 1999 [50] Case series 8/97 –10/97	N= 40 with acoustic neuroma associaed with NF2 Pittsburgh, USA	GK N=35 unilateral	Median follow up 36 mo (6-120) Of n=45 tumours, 36% regressed, 62% unchanged, 2% progressed. In n=10 at >5y, 5 had regressed, 5 unchanged. Clinically, 67% maintained stable results, 33% deteriorated, 2 unrelated deaths Hearing preservation outcomes related to introduction of MRI in planning; pre – MRI 0/5 maintained speech discrimination compared with 6/9 post – MRI introduction	
Suh et al., 2000 [51] Case series 8/89 – 10/95	N= 29 with acoustic neuroma (4 NF2 with bilateral) Cleveland, USA	LINAC	Median follow up 57 mo (9 – 110) 5 unrelated deaths At median 49 mo, local control in 28/29, actuarial 5y control 94% N=4 new/worse permanent facial numbness, N=7 permanent 7th nerve deficits. 5y actuarial rates for TGN, facial neuropathy 15%, 32% Subjective hearing loss or reduction in 74% of n=19	CT used for planning in this series; authors recommend MRI…

Table 2: Studies on SRS treatment of acoustic neuroma (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Thomassin et al., 1998 [52] Case series 7/92 – 5/94	N= 138 with acoustic neuroma, neurofibromatosis cases excluded Marseille, France	GK	N=104 followed up at 3y post SRS Of 85 with some hearing pre – SRS , at 3y 57% had preserved some hearing, with 3.5% improved; 445 deteriorated with 10% losing hearing.	Claim of superiority to microsurgery supported by reference to old publications from other centres.
Uchida et al., 1999 [53] Case series Nagasaki, Japan	N=22 with acoustic neuroma	LINAC	In n=19, loss of contrast on MRI 3-9 mo post SRS, none showed progression. Of remaining 3 tumours, 2 showed progression.	Short –term results, correlation with MRI findings main purpose.
Unger et al., 1999 [54] Case series 4/92 – 12/98	N=56 with acoustic neuroma Graz, Austria	GK; primary treatment	Median follow up 62 mo (48 –80) Control of growth in 56% including shrinkage in 34% Neurological state ameliorated in 54%, worsened in 11% 62% of n=26 with useful hearing pre SRS had hearing preserved; gradual loss in remainder Incomplete facial palsy occurred in 4, persisted in 2.	
Walch et al., 2001 [55] Case series 4/92 – 7/97,	N=79 with acoustic neuroma Graz, Austria	GK, following surgery, n=28	No overall change in facial nerve grading. PTA change from n=10 to n=6 , Grades I - III	Cases with GK as primary treatment in this series considered by Unger et al. Some retrospective data missing.

There appears to be continuing strong opinion from surgical teams that microsurgery is the therapy of choice for most acoustic neuromas. Criticisms made of radiosurgery studies are the relatively short follow up and under-reporting of complications.

Two recent microsurgical studies identified in the course of this assessment were those by Briggs et al. [56] and Kaylie et al. [57]. The series described by Briggs et al. included 121 patients treated surgically between 1994 and 1998. Eleven of them had NF 2. For tumours of all sizes, 90% of patients had good facial function, 7% moderate and 3% poor. There was no mortality and lasting complications were considered minimal (three persons with trigeminal paresthesia and three with cerebellar ataxia are mentioned). Hearing was preserved in 37%.

In the series described by Kaylie et al. [57] patients had microsurgical removal of acoustic neuroma between 1992 and 1998. Facial nerve integrity was preserved in 99%; 95% with small tumours; and 63% with medium tumours had excellent facial nerve function. Overall complication rate was 20%, mostly short term. There were no deaths. Hearing was preserved in 29% of patients with small tumours.

Kaylie and colleagues have also undertaken a comparison of outcomes of treatment for tumours of < 4cm in diameter between 11 microsurgical studies and eight studies using the GK, undertaken between 1990 and 1998 [58]. They conclude that there was no significant difference in facial nerve outcome or hearing preservation but that surgery had significantly lower complication rates (though surgical complications included seven deaths). Surgery also had better tumour control when tumours were totally resected. Results are summarised in Table 3.

Kaylie et al. note that these results do not reflect outcomes from treatments using modern procedures and imaging methods. They also comment on the major difficulty with inconsistent data reporting and call for use of standardised outcomes scales in surgical and SRS reports to permit valid statistical comparison.

Table 3: Comparison of studies using surgery or radiosurgery for acoustic neuroma

	Surgery	SRS (GK)
Patient numbers	2,579	875
% Good facial nerve outcome (% reported)	81.1 (46)	81.1 (82)
Serviceable hearing before treatment (% reported)	42 (55)	40 (63)
Serviceable hearing after treatment	44	44
Complications (studies reporting complications)	21.9% (13/15)	38% (4/8)
Permanent complications	5.3% (include 7 deaths)	16%
Tumour control	97.5% complete removal, 1.6% recurrence rate in n=776 with uncontrolled tumours	For n=805, 32% had tumour regression, 59% no growth, 9% not controlled.

Source: Kaylie et al., 2000 [58]

A survey of members of the American Neurotology Society by Battista and Wiet [59] found that for 12 of 46 patients who had SRS, 12 required follow up microsurgical resection of acoustic neuroma which was technically difficult and associated with poor cranial nerve results.

Also, Luetje [60] notes that spontaneous involution of acoustic neuroma may occur and reports on a series of 47 patients with unilateral untreated tumours who were followed up for 1 – 12.5 y. There was imaging evidence of involution in 13%. The Pittsburgh group found that there had been hearing improvement in 21 out of 487 patients who had radiosurgery during a 10-year interval [61].

Overall, the conclusions on the place of SRS in the management of acoustic neuroma are very similar to those in the 1999 AHFMR report. Microsurgery remains the treatment of choice for many patients. SRS has a useful place in cases where surgery would have an unacceptable risk or would be refused. Long term follow up data on SRS treatment are still comparatively limited, and the methodological basis of the evidence is weak. There is no clear evidence of the superiority of one radiotherapy/radiosurgery treatment over another.

A feature in the literature since the previous AHFMR report has been the number of studies that have used fractionated treatment (FSRT) using linear accelerator technology. This appears to have considerable potential as an alternative to LINAC or GK SRS, but results should be regarded as preliminary. A recent review by Gross and Engenhart-Cabillic [62] gives the comparative summary shown in Table 4. They suggest that in comparison with SRS and neurosurgery, FSRT seems to be more tissue-sparing, though the sources of the information for surgery and SRS are not clearly identified.

Table 4: Comparison of treatments for acoustic neuroma

	SRS, %	Neurosurgery, %	FSRT, %
Response	85-98	92-98	88-100
Recurrence rate	1-10	~7	0-12
Unchanged hearing	30-70	14-57	50-100
Useful hearing	- 85	36-78	66-100
Toxicity to cranial nerves V,VII	0-20	~8	0-16

Source: Gross and Engenhart-Cabillic, [62]

Another trend has been the further use of lower doses in SRS treatment of acoustic neuromas, which has been suggested to improve rates of hearing preservation. However, a potential consequence of lower doses is a higher rate of tumour growth or recurrence, an issue on which there is continuing debate.

Arteriovenous malformations

The 1998 AHFMR report [2] identified seven studies that provided generally weak additional evidence to that considered in earlier HTA assessments. The report concluded that SRS is useful in appropriately selected patients, but there appeared to be a need for long-term follow-up, to include consideration of adverse effects. There was no real indication of the proportion of AVMs that might appropriately be treated by SRS alone or in combination with embolization. In many cases, surgery would remain the preferred option.

Papers that considered treatment of AVMs that were located for the present review are briefly summarised in Table 5. For studies that were concerned primarily with obliteration of AVMs and associated complications of treatment, 14 made use of the GK, one of these making some comparison with microsurgery at the same institution. Seven studies described use of the LINAC and a further study used both LINAC and FSRT. In one study the Rotating Gamma device was used.

Treatment of cavernous malformations was considered in six studies, three based on the GK, two on use of charged particle irradiation, and one on the LINAC. Four studies with a particular focus on management of seizures associated with malformations (3 GK and 1 LINAC) are listed separately in Table 5.

Overall, the evidence on effectiveness of SRS in treatment of AVMs suggests similar conclusions to those of the 1998 report and of recent HTA reports listed in Table 2, though useful further information has emerged on some aspects.

It continues to be difficult to draw firm conclusions on the effectiveness of this technology for treatment of malformations in the absence of controlled trials. Comparisons with microsurgery series are made in some of the papers, but any conclusions have to be treated with some reservation, given inevitable differences in case mix, patient selection criteria and other factors. All of the studies given in Table 5 refer to case series, though in two of them outcomes are reported for more than one treatment method at the same institution. The MSAC and SBU publications referred to in Table 1 have drawn attention to the weakness of the evidence.

The Arteriovenous Malformation Study Group [63] has noted that the rapid changes that have occurred in surgical techniques complicate longitudinal comparison of outcomes. They also make the point that lower reported complication rates after SRS cannot be readily compared with rates for other treatments as adverse effects may be delayed and there have been few long term follow up studies.

Economic consequences of such delay have been considered by Porter et al. [64]. As is widely recognised, SRS takes some time to obliterate an AVM, so that there is an ongoing risk of hemorrhage after irradiation, whereas microsurgery eliminates this risk more quickly and more efficiently. Comments on the Porter et al. paper by persons involved with SRS programs accept this general proposition for easily–resectable

AVMs, while noting that surgical expertise will vary between centres and that not all patients in need of treatment would be considered a good surgical risk.

In a microsurgery series from Germany located for the present assessment that considered 62 patients with small AVMs, there was a 98.4% success rate in removing the AVMs, with 3.2% permanent significant neurological deficits at late follow up [65]. In a consecutive US series of 72 (1985 –1996) reported by Pikus et al. [66], 65 (90%) had a GOS score of 5, three were moderately disabled, and four severely disabled. There was no treatment–related mortality and no patient was in a vegetative state. For all of the 19 patients with AVMs <3cm in diameter there was complete obliteration of the lesion, no new neurological deficits and a good recovery. For the 54 patients (75%) of patients with Spetzler – Martin grades I – III, there was complete angiographic obliteration, 93% reached a GOS score of 5, and one patient had a new neurological deficit. The authors compared their results with those from three SRS series and three other microsurgical series and conclude that microsurgery is superior to SRS in the treatment of smaller, surgically accessible AVMs.

A further difficulty in considering results of AVM treatment with SRS is that in some studies obliteration rates have been over-estimated because of reliance on MRI findings for some cases rather than obtaining confirmation using angiography. This point was made by Howard and Ghersi at a recent conference presentation that evaluated results reported in seven studies of SRS in the treatment of AVMs [67]. They note that obliteration rates appear to range from 36 – 85% at 2y, with most authors reporting 70% or higher. However, when all patients eligible for angiography are considered, actual 2y obliteration rates dropped from an average of 64% (36-81) to 48% (26 – 68%). One of the papers considered by the presentation, by Heffez et al. [68], had made the same point, noting that if all data are considered, the actual 2y obliteration rate is in the range of 40% rather than the commonly reported 80%.

In the papers referred to in Table 5, different approaches seem to have been taken at various centres. Some series have included appropriate consideration of angiographic follow up, in others over-estimation of obliteration seems likely.

However, some useful indications emerge from the papers listed in Table 5. Three of them (1 LINAC, 2 GK) deal with follow up SRS after previously unsuccessful treatment, indicating reasonable success rates for obliteration, though increased risk of radiation – related complications. (A report from Stanford by Chang et al. [69] considers microsurgery following earlier SRS and suggests SRS several years prior to resection appears useful in treating unusually large and complex AVMs as the lesions are significantly less vascular and more easily resected than in patients who have not received SRS.)

Four studies listed in Table 5 report experience in management of AVMs of the brainstem or motor cortex, for which micro surgery is more difficult.

Another paper reports the use of SRS for treating AVMs in children. A further study from Japan reported by Tanaka et al. [70] included 70 adults and 23 children. Complete obliteration rates for the two groups at 1y after SRS were 45% and 74%, and 81% and 94% at 2y. Complications occurred only in adults.

Lindqvist et al. [71] found that there is a small possibility that AVMs may reappear after having been totally occluded after SRS, especially in pediatric patients. They obtained angiograms for 48 patients 5 to 24 y after SRS (using the GK) and 4 to 17 years after the AVMs had been proven to be totally occluded. Ten of the patients developed clinical symptoms attributable to the AVMs or the treatment. There was evidence of AVM nidi at the sites of previously occluded AVMs for two patients and of nidi adjacent to those sites for another two. Three of the four recurrent AVMs were associated with hemorrhaging. All patients who experienced hemorrhaging from previously occluded AVMs were 14 years of age or younger at the time of radiosurgery.

The studies on SRS treatment of cavernous malformations indicated only modest success in management of these lesions, though hemorrhage rates were reduced in some series.

SRS for epilepsy associated with AVMs was more successful, with elimination of reduction in seizures in a high proportion of cases with relatively limited follow up. In addition, in a series of 210 cases reported by Ghossoub et al. [72], seizures completely disappeared in 58% of cases and decreased in 18%. Generalized seizures disappeared in 90.7%, partial secondary generalized seizures in 53.5%, and partial seizures in 39.6%. Success in eliminating seizures was related to their frequency and severity as well as the length of time over which they had occurred prior to SRS.

Pollock et al. [73] report on the feasibility of using a staged volume SRS approach for larger volume AVMs, an approach that would give lower radiation exposure to the surrounding brain.

There is general recognition that microsurgery and SRS should be regarded as complementary approaches to management of AVMs. Surgery is preferred if the lesion can be 'safely ' excised, but appropriate patient selection and level of expertise continue to cause debate. Further information is emerging on longer term complications of SRS. There is no indication that either GK or LINAC is superior to each other. The absence of good quality studies continues.

Table 5: Studies on SRS treatment of arteriovenous malformations

Authors, study design	Patients/Condition	Intervention	Outcomes	Comments
Aoyama et al., 2001 [74] Comparison of cohorts 11/91 – 1/98	N=52 with 53 AVMs Sapporo, Japan	FSRT; N= 26 (4 fractions) LINAC; N=27	Mean follow up 35mo (12-72) Overall actuarial complete obliteration rates at 3 and 5y 64% and 92% (3y values of 79% for <2cm and 50% >2cm). 3y actuarial obliteration ratio 53% for FSRT and 71% for SRS. NSD in time to obliteration 2 radiation – induced necrosis in SRS group.	The two patient groups are not truly comparable because of differences in size and location of AVMs Authors suggest FSRT at least as effective as SRS for obliteration of AVMs
Chang JH et al., 2000 [75] Case series 1288 – 12/99	N=254 of 278 AVMs Seoul, S. Korea	GK n=254 LINAC n = 23 (not analysed) GK only 59%, embolisation in 26%. 14 SRS following failed surgery; 23 repeat SRS; 6 partial resection	Radiological follow up for 128, 101 totally occluded (42% at 24 mo, 57% 36 mo, 78% 48 mo)	Low proportion of patient results reported
Friedman JA et al., 2001 [76] Case series 1991-1998	N=25 with Dural areteriovenous fistula (DAVF)	GK; 20 also had embolisation	2 lost to follow up Symptoms resolved in 20, 87% and improved in 2, 9% Follow up angiography in 17, obliteration in 41%, >90% in 24%, >50% in 35%	Useful presentation of data which includes individual patient details. Authors note persistence of fistula for some patients with consequent risk of hemorrhage. Embolisation, surgery are alternatives
Hadjipanayis CG etal., 2001 [77] Case series 1998-2000	N=33 with motor cortex region AVMs Pittsburgh, USA	GK 1 prior surgery, 9 embolisation	Mean clinical follow up 54mo (10-91) 30 (91%) returned to employment. 1 died of hemorrhage; I had recurrent headaches, 1 persistent paresthesia 17/27 (63%) free of seizures at last follow up (11 with, 6 without drugs) With angiographic follow up at median of 36 mo, 21 complete obliteration (+ 2 by MRI only), 6 >50% reduction in nidus, 8 had second stage SRS of whom 3 had total obliteration subsequently	Authors note expectations of high morbidity with surgical approaches to this type of AVM and briefly review surgical approaches.

Table 5: Studies on SRS treatment of arteriovenous malformations (cont'd)

Authors, study design	Patients/Condition	Intervention	Outcomes	Comments
Karlsson et al., 1998 [78] Case series 1976 – 1994	N= 101 of 112 having follow up SRS for AVMs after initial treatment Stockholm, Sweden	GK	Obliteration: 62% obliterated, 19% decreased significantly, 11% decreased slightly, 9% unchanged. 14 radiation – induced complications; considered to be significantly higher risk than for first treatement SRS. Annual incidence of hemorrhage 1.8% over first 2y, 3 additional at 5,8 and 10y.	Obliteration rate similar to that obtained for first treatment of AVMs.
Kurita et al., 1998 [79] Case series 6/90 – 8/96	N=351 with AVMs Tokyo, Japan	GK	Actuarial obliteration rate 86.5% at 3y. Permanent symptomatic radiation injury 1.4% Hemorrhage post SRS in 3.1 %, 5 deaths (45% mortality)	
Kurita et al., 2000 [80] Case series 7/90 – 10 – 97	N=27 with brain stem AVMs Tokyo, Japan	GK	Mean follow up 52.2 mo (6-96), 1 lost to follow up. Actuarial 5y survival 87.5% Neurological signs – 8 improved symptom free, 4 improved, 3 no change. 5 deaths, 4 from 5 hemorrhages Obliteration in 44% (angio confirmed), incomplete in 56%. Standard dose cases (18 –20 Gy) had actuarial 3y rate of 69.4% compared with 14.3% for low dose (<18Gy)	
Levy et al., 2000 [81] Consecutive case series 8/87 – 8/96	N= 53 children (median 12y, 2 –17) with AVMs Pittsburgh, USA	GK	Median follow up post SRS 36 mo (6 –103) Complete obliteration in 80% with volumes < 3mL, 64.7% for vols 3-10 mL, single > 10mL not obliterated. 93% returned to previous activity levels post SRS 2.5% hemorrhaging episodes /y	N=10 had second SRS Angiography to confirm obliteration in 24, MRI used for others
Lind et al., 2001 [82] Case series 7/94 – 12/97	N=28 with AVMs Dunedin, New Zealand	LINAC; Prior surgery in 6, XRT in 2, embolisation in 1.	Median follow up 15 mo MRI evidence of obliteration in 9/11 with >2y follow up, confirmed with angiography in 8. 1 post SRS hemorrhage, 5 with persisting neurological side effects.	Preliminary data from early experience at this site

Table 5: Studies on SRS treatment of arteriovenous malformations (cont'd)

Authors, study design	Patients/Condition	Intervention	Outcomes	Comments
Maeswa et al., 2000 [83] Case series , retrospective 4/91 – 10/96	N=41 of 54 with AVMs and >2y follow up who had repeated SRS (persistent nidus after 3y from initial tretament) Pittsburgh, USA	GK	Follow up angiography >2y after second SRS available for 30/41; obliteration 70%, reduction in 25%, remaining case obliteration after third SRS For remaining 11 cases, obliteration 70%, based on MRI findings 2 patients had hemorrhage from AVMs	
Massager et al., 2000 [84] Case series from two centres, retrospective analysis 92-97 and 87 – 99)	N=87 with brainstem AVMs, outcomes reported for those with follow up of >2y Marseille, France and Pittsburgh, USA	GK	Mean follow up 3.2 y (6mo – 10y). For those with follow up of >2y: In n=42, symptoms improved in 5%, stable in 90%, worsened in 5% In n=46, obliteration rate 63% at 2 y (some by MRI), 73% at 3y (all angiography)	Results from individual centres not reported;
Miyawaki et al., 1999 [85] Consecutive case series 3/98 – 9/91	N=73 with intracranial AVMs, 51% >3cm San Franciso, USA	LINAC N=43 had prior embolisation procedures	Results reported in different ways, refer to n=60. Overall obliteration rate 64%, 47% and 30% depending on definitions; latter refers to angiographic confirmation for obliteration and all failures. Obliteration rates decreased with increasing AVM size; given as <4 mL, 67%; 4-13.9mL, 58%, >13.9mL 23% 13/73 required intervention for treatment-related complications; I treatment – related fatality due to planning error; 12/73 (14%) clinically significant hemorrhages, 5 fatal.	Authors comment on difficulties with reporting methods used for obliteration rates
Mobin et al., 1999 [86] Selection from case series 1990 – 1997	N=48, 50 AVMs Los Angeles, USA	LINAC 36% of AVMs embolised prior to SRS	Mean follow up 18mo (6-49) 45% obliteration of AVM (confirmed with angiography), 44% reduced; 20% unchanged	Focus of the paper is on MRI signal as predictor of response Patients selected on basis of availability of imaging follow up

Table 5: Studies on SRS treatment of arteriovenous malformations (cont'd)

Authors, study design	Patients/Condition	Intervention	Outcomes	Comments
Pan et al., 2000 [87] Case series 3/93 – 3/99	N= 240 with AVMS, 76 with AVMs > 10cm3 Taipei, Taiwan	GK	Actuarial obliteration rates at 40mo for AVMs of <10 mL, 10-15 and < 15 mL were 92%, 80% and 50%. Epilepsy improved in 67% of n=70, no change in 23% Neurological status unchanged/improved in 94% 4.% post SRS hemorrhage (one death), 3.3% permanent morbidity,	
Pelissou –Guyotat et al., 1997 [88] Case series 1990 – 1995	N= 34 with low grade AVMs Lyon, France	LINAC 19 had prior embolisation or surgery	Angiographic follow up at minimum of 2y Obliteration rates: 100% SRS, SRS + surgery, 76% embolisation +SRS 100% Surgery + embolisation, 82% surgery; 65 embolisation. No deficit in 91% of SRS cases, 71% of overall series, major deficits 3% and 7%, vegetative/death nil and 4%	Surgical cases were higher grade AVMs overrall, but exact details not given
Regis et al, 2001 [89] Case series, retrospective review 07/92 –12/99.	N= 45 with AVMs in brain stem Marseille, France	GK first treatment for n= 29;	Mean follow up 18 mo in n= 25 patients. For n=13 obliteration rate was 82% N=2 with permanent neurological deficits; n=2 hemorrhage 12-36 mo post SRS	Some of these cases would have been included in the study of Massager et al.
Ross et al., 2000 [90] Case series 1995 -	N= 36 with 37 AVMs Ann Arbor, USA	LINAC	Mean follow up 25 mo (1-49) Obliteration (angiography) in 35% - include n=4 size D, 10 –25 mL - + 11% on MRI only, 1 retreatment , remainder <2y or lost to follow up No hemorrhages post SRS; complications transient	

Table 5: Studies on SRS treatment of arteriovenous malformations (cont'd)

Authors, study design	Patients/Condition	Intervention	Outcomes	Comments
Sasaki et al., 1998 [91] Retrospective review of treatment cohorts 1971 – 1995	N= 101 with AVMs Tokyo, Japan	GK, n= 66 Surgery, n= 15 Embolisation = 5 Conservative treatment , n=15	GK: actuarial obliteration rate 85.7% at 2.5y. Treatment – associated morbidity 6.7%; 3 permanent neurological deficits, 3 hemorrhage. Surgery: Permanent motor function deterioration in 20% Embolisation: Morbidity and mortality 40% and 20% Conservative: Hemorrhage in 71.4%, morbidity and mortality rates 7.1%, 42.9% mean follow up 6.6y	
Schlienger et al., 2001 [92] Case series 1989 – 2000	N=39 with AVMs previously treated by SRS France CHK	LINAC	For n=28. obliteration rate 60.7%. Nine patients bled between the two SRS procedures. 4 new deficits occurred after the second SRS.	
Vladyka et al, 1997 [93] Case series 3y period	N=134 with AVMs Prague, Czech Republic	GK Prior surgery in 34, embolisation in 12	Angiographic follow up at 12 – 30 mo Total obliteration in 70%, actuarial 2y 90 .5%; clinical improvement noted in further 22% 1.5% hemorrhage post SRS, no sequelae	
Wolbers et al., 1999 [94] Prospective case series, comparison with surgery 11/91 – 12/95	N=29 with 30 AVMs Amsterdam, The Netherlands	LINAC	Follow up angiography at mean 35 mo (24 – 70), data for n=27 Obliteration in 71%. No permanent neurological deficit.	Individual patient details provided
Yamamoto et al., 1998 [95] Case series 1978 –94	N = 53 with AVMs Tokyo, Japan	GK	Complete obliteration in 60.4% at 2y (angiography); 34 % shrinkage, but persisting at mean 1 mo – of these 1 death from rebleeding complication, 1 from angio complication, I surgery for cyst enlargement, 7 second SRS 4/7 obtained complete obliteration 5 radiation –related morbidities (9.4%) 3 at 5.5 and 7y post SRS; further 9.4% asymptomatic but with radiation – related adverse effects on imaging.	Earlier paper in this series considered in previous AHFMR assessment Focus on long term follow up

Table 5: Studies on SRS treatment of arteriovenous malformations (cont'd)

Authors, study design	Patients/Condition	Intervention	Outcomes	Comments
Zhou et al., 2000 [96] Case series 11/96 –5/00	N= 132 with AVMs (80% grade II or higher) Beijing, China	Rotating Gamma System 27 previous surgery, embolisation in 34	Mean follow up 18.4 mo (5-44) for n= 106. In n=34 with seizures pre SRS, 18% complete control, 32% improved, 50% no change. Angiography at 1y in n=57 showed total obliteration in 42%, partial in 58%, no change in one case At 2y in n=27, total obliteration in 78% Post SRS AVM rupture in 5 cases	
Cavernous malformations				
Amin-Hanjani et al., 1998 [97] Retrospeective review of case series 1977-1993	N=95 with 98 AOVMs Boston, USA	Proton beam	Mean follow up 5.4y (0.3 – 12.3) In 73 cases where there had been hemorrhage before SRS, annual hemorrhage rates decreased from 17.3%/ lesion to 4.5%/lesion after latency period of 2y Neurological disability worsened overall (Rankin scores) n=47 experienced neurological deterioration. Signs of radiation-induced injury in 26 cases, 16 of these permanent deficits	Authors note need to balance success with hemorrhage contro l with risk of radiation – induced injury, further information needed before SRS can be claimed as superior to conservative management
Chang SD et al., 1998 [98] Case series	N= 57 with AOVMs Stanford/ Loma Linda, USA	Helium ion (n=47) or LINAC (n=10)	Mean follow up 7.5y 32% had hemorrhage after SRS. Initial annual bleeding rate 12.3%, rate after 2y was 1.9% NSD in before – after KPS scores, Drake scale scores post SRS excellent 44%, good 42%, poor 5%, dead 9% 3/5 deaths unrelated to AOVM or SRS	Combined outcomes reported for both SRS methods Note need for longer term follow up.
Karlsson et al., 1998 [99] Case series, 1985 – 1996	N=22 of 23 with cavernous malformations Stockholm, Sweden	GK, 15 Gy to periphery in first half of series, lower doses subsequently	9/22 had hemorrhage post SRS, 6/22 radiation – induced complication (both in 2 cases). Subsequent surgery for removal in n=6	Authors state it could not be concluded whether SRS affects the natural course of a CM. Conclude that the high incidence of radiation-induced complications does not seem to justify the limited protection the treatment may afford in only exceptional cases

Table 5: Studies on SRS treatment of arteriovenous malformations (cont'd)

Authors, study design	Patients/Condition	Intervention	Outcomes	Comments
Liščák et al., 2000 [100] Case series 1992 – 1998	N= 25 of 26 with brainstem cavernomas Prague, Czech Republic	GK	MRI/CT on 24/25 at median 24 mo (6 –48) decrease of cavernoma size was observed in 33%, others unchanged. 4% risk of rebleeding before SRS, 6.8% after, difference said to be NSS. Improvement of neurodeficit in 43% at median 8 mo after SRS. 2 deaths from rebleeding 6 and 51 mo post SRS.	Considered that SRS of brain stem cavernomas indicated when there was bleeding in the history or progressive neurodeficit and microsurgery was considered too risky.
Tsien et al., 2001 [101] Case series 1987 – 1996	N=21 with angiographically occult AVMs Montreal, Canada	LINAC Prior shunt in 2, partial resection in 3, XRT in 1	Median follow up 77 mo (4 – 141) on n=20 Annual hemorrhage rate 3.2%, compared to a rate of 29.8% prior to SRS N=16 had stable or improved neurological signs. N=1 had progressive neurological deficit	
Zhang et al., [102] Case series 1377 1994 –1995	N=53 with cavernous hemangiomas Shanghai, China	GK	Mean follow-up 4.2 y for n=51. Shrinkage of lesion in n= 19. In 18 /28 patients whose chief complaint was seizures, decrease in seizure frequency. 5/23 patients with hemorrhage had rebleeding 4 - 39 mo after SRS. N=17 with hemangioma at frontal or parietal lobe had neurological disability, severe in 5.	
Seizure associated with AVMs				
Bartolemi et al., 1999 [103] Retrospective data from 5 centres, 1991 – 97	Epilepsy associated with cavernous hemangiomas, drug resistant, duration 7.5y N=53 from France, Austria, Japan, UK, Czech Republic, 49 with sufficent ddetail to follow up	GK Mean delay of 4 mo	Mean follow up 23.7 mo Seizure free 26%, significant decrease 20%, little or no improvement 26%. 7 had major radiation edema; I speech impairment, 1 hemiparesis in first y, both recovered	Data by centre are not given. Authors mention reports of surgical success rates of 20 – 8% (not separately evaluated). They also note the lack of convincing efficacy of GK in reduction of hemorrhage from CH

Table 5: Studies on SRS treatment of arteriovenous malformations (cont'd)

Authors, study design	Patients/Condition	Intervention	Outcomes	Comments
Eisenschenk et al., 1998 [104] Retrospective case series over 4y Structured interview, clinical follow up.	N=100 AVM cases treated with SRS, of whom 33 had epilepsy Gainesville, USA	LINAC Anticonvulsant unchanged after SRS	Mean follow up 26mo (11 – 54) 19/32 seizure free (9/13 complex; 3/8 simple partial; 7/11 general tonic/clonic) and 6/32 had reduction of >75%. 15/19 seizure free by 6 mo For N=14, angiographic follow up at 2y indicated 9/14 had complete thrombosis, 6 seizure free. Of remaining 5, 4 seizure free.	Limited details of interview approaches
Kida et al., 2000 [105] Case series Since 1991	N=79 with AVMs and convulsive sezure prior to SRS, 58 (group A) as an initial symptom, 21 (group B) following hemorrhage Komaki City, Japan	GK	Mean follow up 24 mo In group A, 70.8% seizure free, 20.8% decreased rate, 8.4% unchanged or increased. Corresponding values for group B 37.5%, 25%, 37.5%. Good seizure control in 94.7% of completely obliterated AVMs and 77.1% incompletely obliterated lesions, difference not SS.	
Regis et al., 2000 [106] Retrospective review of records from 5 centres 1991 – 1997	N=49 with epilepsy associated with cavernous malformation Marseille, France; Graz, Austria; Sheffield, UK, Prague, Czech Republic; Komaki City, Japan	GK	Mean follow up 24 mo 3% seizure free, decrease in 20%, remainder little or no change.	

Trigeminal neuralgia

The 1998 AHFMR report gave brief consideration to the use of SRS for trigeminal neuralgia (TGN), reviewing four recent papers (two on SRS and two on surgical approaches) noting that SRS had been used for many years in the treatment of this condition. Surgical procedures appeared to offer the best outcomes.

Studies of SRS in treatment of TGN are listed in Table 6. All of these made use of the GK. One was an RCT and the rest were case series. The RCT addressed a choice of treatment procedures and indicated that increasing treatment volume was not appropriate. This and the other studies considered treatment of idiopathic TGN or facial pain secondary to a tumour.

Findings in the studies include initial pain relief in high proportions of patients, but also high rates of recurrence of pain and neurological side effects.

There are a number of options for treatment of TGN [107] and the place of SRS does not seem to be established. If drug treatment is ineffective, microvascular decompression has been recommended for younger, fit patients and percutaneous radiofrequency thermorhizotomy (PRT) for older patients and for those unwilling to have surgery [107]. Kanpolat and Savas [108], and Kao [109], have drawn attention to the effectiveness of PRT and of microvascular decompression as indicated by large series with long term follow up, with repeat procedures for cases where there is recurrence of pain. Recent papers by Kanpolat et al. [110], Mathews and Scrivani [111], and Scrivani et al. [112] have reported on long term results with PRT, and Tronnier et al. have compared PRT with microvascular decompression, recommending the latter as the treatment of choice in otherwise healthy people whose pain is not controlled by medication [113].

Table 6: Studies on SRS treatment of trigeminal neuralgia and other causes of facial pain

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Brisman and Mooji, 2000 [114]; Brisman 2000 [115] Case series 05/98 – 02/00 Responses from patient questionnaire (not described)	N=172, TGN not controlled with medication. New York, USA	GK, 82 as primary intervention, 90 following surgery	126 followed up at 6mo, 84 at 12 mo. For 48 with volumes >20mL, excellent pain relief for 56% at 6mo, 50% at 12 mo. For 78 with volumes <20mL, corresponding values 32% and 27%. Pain relief less likely for those who also had MS 12 mo values for good or excellent pain relief 85% and 79% for those with no MS, SRS only and SRS + surgery. Values for those with MS 57% and 38%	Author notes that GK as primary treatment provided better relief. However, from details given of division of TG nerve in which pain was experienced, patient groups may have been different. High drop out rate for follow up.
Flickinger et al., 2001 [116] RCT Assessors blinded to treatment allocation	N=87 with TGN Pittsburgh and Rochester MN, USA	GK; patients randomised to SRS with either I or 2 isocenters	Median follow up 26 mo (1-36) Complete pain relief in 66%, without medication in 55%. Median time 30 mo (1wk-17mo) post SRS. Partial improvement in 17%, no benefit 17%. Relapse in 42% of 72 responding patients , median 12 mo (2-31) after pain relief. Less frequent in two isocenter treated group but not SS. New or increased trigeminal dysfunction in 24%, 2y actuarial rate 33% for 1 isocenter group, 17% for 2 isocenter group.	Conclude that increasing treatment volume to include longer nerve length does not significantly improve pain relief but may increase complications
Han et al., 1999 [117] Case series, follow up data using questionnaire	43 patients (25F, 18M, mean age 66y) with TGN who had failed drug treatment. 35 idiopathic, 8 MS – related. 22/43 had undergone 46 prior invasive treatments. Phoenix, USA	GK Mean time from initial diagnosis to treatment 10.9 y.	Mean follow up 9 mo (range 2-23) 15 (35%) had no TGN-related pain, took no medication; 3(7%) had occasional pain, did not need medication; 15 (35%) improved pain, controlled on medication; 10 (23%) failed treatment (no relief or pain not controlled with medication). Mean time to initial pain relief 31d (1-115); mean time to maximal relief 78 d.	100% response to questionnaire, not reported if all questions were answered. No individual patient data or clinical details; wide range for follow up.

Table 6: Studies on SRS treatment of trigeminal neuralgia and other causes of facial pain (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Kondziolka et al., 1998 [118] Case series	N=106 with refractory TGN (from consecutive series of 121) Pittsburgh, USA	GK	Median follow up 18 mo (6-48) Initial improvement in 86% At last follow up, no pain in 60%, 50 –90% decrease in 17%, <50% relief in 23%. Relapse in 10% of 64 who attained initial complete relief. 10% developed new or increased facial paresthesias after SRS.	Continuation of series considered in 1998 AHFMR report
Maeswa et al., 2001 [119] Consecutive case series	N= 220 with idiopathic TGN (excluded 25 non-idiopathic cases and 19 who had repeat SRS treatment) Pittsburgh, USA	GK Previous surgery on 61.4%, primary treatment on remainder	Median follow up 24mo (6-78) Pain: 21.4% additional surgery because of poor control 6 mo results; excellent or good 63.2. fair 19.1%, latest follow up: 55% and 14% Time to >50% pain relief 2mo, recurrence of pain mean 15.4 mo 7.8% developed increased parethesias/ numbness lasting >6 mo	Correspondence on this study criticised relatively short term follow up , classification of "good" where medication was still being taken , and drew attention to good outcomes from percutaneous controlled radiofrequency rhizotomy [120]
Nicol et al., 2000 [121] Case series	N=42 with TGN Lexington, USA	GK, 12 had prior surgery	Median follow up 14mo (2-30) 73.8% complete relief, 21.4% 50 – 99% relief (good) n=7 had increased or new facial numbness	Authors claim that 90Gy is safe and effective dose, note need for longer follow up.
Pollock et al., 2001 [122] Case series 4/97 –12/99	N= 68 with idiopathic TGN Rochester, MN, USA	GK 40% 70Gy 60% 90 Gy	Mean follow up 14.4 mo (2-36) 41% of low dose group and 61% of high dose group remained pain free. Additional surgery on 44% low dose and 20% high dose. Permanent trigeminal nerve dysfunction in 15% low dose, 54% high dose (authors suggest limiting dose to< 90Gy)	In a separate paper [123] authors describe N=26 of 100 treated between the same dates who required further intervention because of lack of relief or recurrence; n=10 had second SRS After second SRS, initially 9/10 pain free, 8 remained pain free at median 15mo follow up, but all developed minor neurological dysfunction1-4wk

Table 6: Studies on SRS treatment of trigeminal neuralgia and other causes of facial pain (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Rogers et al., 2000 [124] Consecutive case series Patient questionnaires to assess pain 3/97 – 3/99	N=54 with trigeminal neuralgia and follow up of > 3mo Phoenix, USA	GK; n=29 as first treatment	Initial improvement in pain level in 96%; no pain or occasional pain in 41%; 48% some pain, controlled with medication. Median delay from SRS 15d (<1-192) Maximal relief median 63d (<1 – 253) Crude pain recurrence rate 21%, median time 6.7 mo (1-20) Actuarial 2.5y pain recurrence 36% Those with better initial responses less likely to develop recurrent pain	
Young RF et al., 1998 [125] Case series	N=110 with TGN Seattle, USA	GK 38 prior surgery	Mean follow up 19.8 mo(4-49) Initial response 76.4% excellent (pain free) 11.8% good, 11.8% failures. Mean latency to pain relief 14d Recurrent pain in 34%, 15.5 % in those without what was considered atypical pain; 2.7% had delayed loss of facial sensation	
Secondary facial pain				
Chang JW et al., 1999 [126] Case series, 11/91 to 10/98	N=27 with facial pain secondary to tumor Seoul, S Korea	GK in 26, LINAC in 1 14 SRS as primary, 14 microsurgery prior to SRS	Initial pain improvement in 24/27, 86%. Time to initial pain improvement 6.3 mo (0.2 – 49) 12/24 had recurrence (10.3 mo). For those with continuing pain relief 5/12 pain free, 7/12 pain reduction.	Conclude that secondary facial pain is less responsive to SRS than is TGN NS correlation between pain relief and tumour volume reduction.
Pollock et al., 2000 [127] Case series 1/90 – 10/97	N=24 with tumour – related trigeminal pain (9 TGN, 13 neuropathy) Rochester, MN, USA	GK	Median follow up 62 mo for meningioma cases, 25 mo for those with malignant cranial base tumours. 50% initially pain free, decreased in 46%; similar responses for tumour types and trigeminal condition	Details given of individual patients

Table 6: Studies on SRS treatment of trigeminal neuralgia and other causes of facial pain (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Regis et al., 2001 [128] Case series 7/92 – 6/97	N=53 with TGN secondary to middle or posterior fossa tumours Marseille, France	GK	Median follow up 55 mo For n=51 where data available 78.4% pain free, 13.7% improved, 7.8% treatment failed Response in <3mo for 71%, >3mo 29% Recurrence in 13.3% of n=45 for whom data available Tumour growth control for 15/16 meningioma Initial control of all cranial base carcinomas but 6/8 then progressed with pain recurrence or worsening in 4	Individual patient details listed in an earlier publication on this series [129]

Brain metastases

The 1998 AHFMR assessment concluded that the role of SRS in treatment of brain metastases was still not well defined. SRS appeared to have a place in the management of appropriately selected patients, and to be a useful option when the patient was not a candidate for surgery.

The AHFMR publication commented that a number of reports on SRS treatment of brain metastasis made comparison with the results of two RCTs undertaken by Patchell et al. [130] and Noordijk et al. [131]. These compared the results of radiotherapy alone with radiotherapy plus surgery. Both studies provided good to fair evidence that combined radiotherapy and surgery gave better survival and functional independence than radiotherapy alone. The results from these two RCTs were cited in a number of the reports on SRS of brain metastases to provide a comparison of treatments. The SRS studies were relying on data from small trials at different centres and with different populations. Many of the SRS studies were therefore be classified as uncontrolled case series, giving a fair to poor level of evidence of outcomes. The same point has been made in the assessment report of MSAC [18].

Overall, the results from eight studies reviewed in the AHFMR assessment suggested survival periods following SRS to be comparable to the "comparison" studies, with indications of improved functional independence and quality of life. There were high levels of local control (an intermediate measure) in a number of studies. Substantially worse outcomes were obtained for patients who had more than two detectable metastases.

There have been some recent overviews of this area of application of SRS. The review by the Health Technology Assessment program of the US Department of Veterans' Affairs [20] referred to in Table 1 considered literature from 1991 to November 1997, including 13 case series (1,276 patients) of which two were prospective. Local control (10 studies) varied from 47 to 100% and actuarial survival from 28.4% (initial and recurrent treatment) to 53% (initial treatment, one metastasis). Median survival was from 26 to 56 weeks. The authors concluded that while SRS was a relatively safe and effective technology for treating brain metastases in selected patients, and seemed to offer greater survival than XRT, lack of data from high quality studies precluded any definitive assessment of its effectiveness relative to standard treatment.

Somewhat similar conclusions were reached in reviews by Boyd and Mehta [132] and by Becker et al. [133]. The first considered 21 studies and reported composite data indicating a local control rate of 83% and median survival of 9.6 months, suggested as comparable with results in recent surgical reports. However, these were the studies by Patchell et al. and Noordijk et al., and the same criticisms made in the 1998 AHFMR report apply. The review by Becker et al. considered 10 studies and estimated local control rates of 85– 95%, recurrence rates of 6-15%, median survival of 6-12 mo and side effects in 3-15%

of cases. It is suggested that SRS and surgical series have attained similar results, but no convincing evidence is presented.

Studies located for this assessment are listed in Table 7. There were 14 LINAC – based studies, four that used FSRT (plus small numbers with this approach in one of the LINAC studies) and 26 studies that used the GK. In addition, one study reported results from both LINAC and GK treatments and another reported combined experience from ten centres, four using LINAC and six GK.

Most of the reports were of case series, but there was one RCT, three case control studies and six where some comparison was made between different treatments used in case series (one was a prospective comparison of treatments). The study reporting experience from ten centres compared findings with those in the RTOG data base.

The RCT, by the Pittsburgh group, compared treatment with SRS +WBRT and with WBRT alone. The trial was stopped before recruitment was complete when better results for time to local failure were established for the combined treatment group. There was also a trend to improved survival in the combined treatment group, but statistical significance was not reached.

These results indicating superiority of SRS plus conventional radiotherapy over radiotherapy alone are supported by findings from some of the other comparative studies located. However, the question of whether SRS + WBRT is superior to SRS alone does not seem to have been resolved, with findings varying from centre to centre in studies of limited methodological quality.

The studies that used fractionated doses appear to have achieved reasonable short term outcomes, but the results are preliminary; longer follow up and additional patient numbers are required. A small study by Ikushima et al. [134] (n=10 for FSRT, 11 for surgery +WBRT and 14 for WBRT) indicated that in patients with brain metastases from renal cell carcinoma, FSRT offered better tumour control and survival than either conventional radiotherapy or surgery followed by conventional radiotherapy.

Of some interest is the report by Chidel et al. [135] of experience at the Mayo Clinic where both LINAC and GK have been used. There was no significant difference in rates of local or distant brain relapse between patients treated by LINAC and those treated by GK.

Comparisons of SRS and microsurgery seem inconclusive, give differences in case selection, small numbers and other methodological limitations.

The main focus of the studies is on local control of metastases and survival. Several papers also report and comment on clinical/neurological status and a few deal more specifically with QOL issues. Indications are that SRS achieves worthwhile benefits, though comparative performance with surgical management is unclear. Several papers report results suggesting that total tumour volume is of more prognostic significance than the number of metastases.

Table 7: Studies on treatment of brain metastases

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Alleyne et al., 1997[136] Case series	N= 40 with 41 metastatic lesions Atlanta, USA	LINAC with patient rotator Prior WBRT in 25, surgery in 11	Clinical complete or partial response in 10%, stable in 23%, progressive disease in 67% Median survival time 9 mo	Preliminary results, part of study that considered other conditions
Amendola et al., 2000 [137] Case series 11/93 – 3/99	N=22 with brain metastases from renal cell carcinoma, 18 with multiple lesions Miami, USA	GK Previous WBRT in n=11	Median survival 8.4 mo (0.8 - >63 mo) Overall actuarial survival 55% at 6mo, 18% at 24 mo Local control in 91% I case of radiation necrosis	
Amendola et al., 2000 [138] Case series 12/93 – 7/98	N=68 with multiple brain metastases from breast carcinoma; average 8 sites/patient Miami, USA	GK; SRS sole treatment in n=30, followed failed WBRT in n=38 including 2 with previous GK	Median follow up 7.8 mo (0.2 – 42.8) Mean actuarial survival 7.8 mo, 32% at 1y. For n=15 with single metastasis, median survival was 7.7 mo. Overall local control 94%, actuarial local control 44% at 1y, 36% at 2y, freedom from intracranial relapse 9.6 mo Local control SS higher for smaller lesions. 3/68, 4.4%, developed brain necrosis after SRS	Cite prolongation of median survival to about 4mo with WBRT as a comparator. Average sites per treatment in this series was 5
Chidel et al., 2000 [135] Case series, retrospective review, with comparison of treatment cohorts 8/89 – 12/98	N = 135 with newly diagnosed brain metastases Cleveland, USA	LINAC, N=73 GK, N = 62 N=57 also received WBRT at initial presentation	Median overall survival 7.9 mo (1.1 – 90.1). Those receiving WBRT with SRS had median survival 6.4 mo v 10.5 mo for SRS alone, reflects worse pre-treatment characteristics. Intracranial disease - free survival SS improved with adjuvant WBRT. No SS difference in local or distant brain relapse between patients treated by LINAC and those treated by GK. (Local relapse: 20.5% LINAC, 22.5% GK. Distant relapse 28.8% LINAC, 29.0% GK) Only RPA class was an independent predictor for overall survival.	

Table 7: Studies on treatment of brain metastases (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Cho et al., 1998 [139] Case series 3/91 – 5/95	N= 73 with brain metastasis; those dying at <3mo (n=11) excluded from analysis of progression – free survival. Minneapolis, USA	LINAC	Actuarial survival rates 32% at 1y, 21% at 2y, median 7.8 mo from time of SRS. Local progression – free survival 80% at 1 and 2y; regional PFS 58% 1y, 44% 2y; RPFS at 2y 66% for n=30 with single metastasis, 19% for n=32 with multiple metastases Minimal post SRS morbidity.	Purpose of the study was to evaluate prognostic factors that predict local – regional control and survival. There was worse prognosis with larger tumours, multiplicity of metastases and infratentorial location of metastases. Absence of extra cranial disease, KPS>70 and single metastasis were significant predictors of longer survival. Authors suggest careful selection of patients for SRS is warranted
Cmelak et al., 1997 [140] Case series 1989 -95	N=36 with 48 skull base metastases or local recurrence from head 7 neck cancers Stanford, USA	LINAC	Median follow up 9 mo (1-60) Local control in 69% of lesions, actuarial local control 53% at 2y	Paper also describes n=11 with primary nasopharyngeal carcinoma, not considered here.
Fernandez-Vicioso et al., 1997 [141] Case series, treatments between 03/1990 and 01/1995, retrospective review, analysis of prognostic factors	48 patients with solitary brain metastasis, 11/48 treated after relapse following WBRT or surgery.	LINAC WBRT given to 38 patients, Surgical debulking in 13 Chemotherapy/hormonal treatment for 16	Local control in 39 (81%) Median survival 8 mo; 37% survival at 1y, 17 at risk; 17% at 2y, 6 at risk.	
Feuvret et al., 1999 [142] Case series 1/94 – 12/97	N=26 with 43 metastases (7 with extra cranial metastases) Paris, France	LINAC	Overall local control rate 90.5%. Median survival 15 mo. Actuarial local control rates 85% at 1y, 75% at 2y.	
Firlik et al., 2000 [143] Case series 1990 -1997	N= 30 with 58 brain metastases from breast carcinoma, Pittsburgh, USA	GK	Mean follow up 13mo Median survival 13mo after SRS, 18 mo from diagnosis Multiple metastases increased the death rate by a factor of 3.38 Local control achieved in 43/46 metastases at mean follow up of 9 mo (1-31)	

Table 7: Studies on treatment of brain metastases (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Fukuoka et al., 1996 [144] Case series, from 5/91	N=130 with brain metastases, 655 with multiple lesions Sapporo, Japan	GK	Mean follow up 9mo (1-49) New distant lesions in 27% Median survival 8mo ; 1y survival rate 30%	2y reported as 26% but from graph appears to have been lower.
Garell et al., 1999 [145] Case control study 1/92 – 12/96,	N= 45 with brain metastases Iowa City, USA	LINAC, n=8 Microsurgery n=37 87.5% and 94.6%, respectively, also had WBRT	Follow up until 12//97. Mean follow up 9.8 and 9.3 mo for the two groups. Median survival 12.5mo in SRS group (2-56), 8 mo (2-38) in surgical group Actuarial 1y survival rates 50% and 32%, not SS.	Authors note limitations of retrospective approach. Small sample limits usefulness.
Goyal et al., 2000 [146] Consecutive case series 1991 –1998	N=29 with 66 metastases from renal carcinoma Cleveland, USA	GK; sole treatment in n=13; others followed WBRT or surgery	Median survival from diagnosis 10 mo Of n=23 with follow up imaging, tumours recurred in 9%	
Grob et al., 1998 [147] Case series, consecutive cases	N=35, 4 single metastasis, 13 single brain metastasis + others, 18 multiple brain metastases Marseille, France	GK Post SRS, 23 received fotemustine. Several drugs used for those with extra - cerebral metastases.	Of 21 patients with neurological symptoms, 9.6% recovered, 33% improved, 28.6% unchanged, 14.35 deteriorated (information missing for 3 patients) Median survival 7mo (22 mo for single metastasis, 7.5 mo if metastases elsewhere; 4.1 mo multiple brain metastases) NSD in survival for those who received fotemustine	Authors note benefits obtained using SRS alone, without WBRT; note need for randomised trials
Grosu et al., 2001 [148] Case series 7/95 – 7/98	N=60 with 80 brain metastases; 35 had single lesions Munich, Germany	LINAC	Mean follow up 13 mo Tumour control 90% at 12mo, 73% at 24 mo Compared with literature values, SRS achieved higher local control and fewer side effects than WBRT, and had lower morbidity and mortality than surgery	

Table 7: Studies on treatment of brain metastases (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Hoffman et al., 2001 [149] Case series, retrospective review 9/91 – 12/98	N=113 with brain metastases from lung carcinoma San Francisco, USA	GK WBRT also for 19/60 with newly diagnosed metastases. SRS for recurrence after previous WBRT in n=53	Median follow up 27.7 mo. Median survival after SRS 12.0 mo; 13.9 mo for SRS only, 14.5 mo SRS +WBRT, 10.0 mo SRS for recurrent . Actuarial 1y probabilities 58%,53% and 40% Freedom from progression studies in 90/113. Median 1y local FFP 81%,86% and 65% for these groups	
Huang C-F et al., 1999 [150] Case series To 4/98	N=26 with 27 brainstem metastases Other metastases (34) in 14 patients Pittsburgh, USA	GK All with newly diagnosed disease had fractionated WBRT; 15 SRS after that, 4 1-9 mo later	Local control rate of brainstem tumours 95% 10/20 with brainstem neurological deficits improved, 8 remained stable, 2 deteriorated; 3/5 with non brainstem deficits also improved 22 deaths 1-33 mo post SRS; median survival time 11 mo after diagnosis; 1y actuarial survival rates 21.7% post SRS, 29.9% post diagnosis	
Huber et al., 2001 [151] Consecutive case series 9/96 –11/97	N= 48 with 87 metastases Heidelberg, Germany	LINAC	Median follow up 8 mo Median actuarial survival 9 mo, 1 and 2y rates 30% and 18% Local control in 6/48 patients, 81/87 metastases	
Jyothirmayi et al., 2001 [152] Case series 1990 - 1997	N=96 with 106 solitary brain metastases, 84 with KPS >70 London, UK	LINAC, mean 20Gy in two fractions for n=73, others higher or more fractions. Initial treatment in n=38, at recurrence in n=29 following WBRT and/or surgery, mean interval prior to SRS 8mo	Median survival 9mo Radiological response in 37%, 56% stable, 7% progressive disease Neurological deficit improved in 51% (32% complete,19% partial), stable in 14%, deteriorated in 14%, not assessed in 22% Based on RPA classification, median survival for favourable cases 15 mo, intermediate prognosis 8 mo, poor 2mo	Refer to their approach as stereotactic radiotherapy/ radiosurgery

Table 7: Studies on treatment of brain metastases (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Kato et al., 1996 [153] Consecutive case series	N=51 with metastatic tumours (44 single, 7 2 or 3) Sapporo, Japan	LINAC	Median survival 10 mo. Complete response 39%, partial 41%, minimal 16% Local control 87.5% for tumours <2cm, 60% for larger	
Kim YS et al., 1997 [154] Case series 1998 - 1995	N= 77 with metastases from NSCLC Pittsburgh, USA	GK N=71 WBRT N=16 surgery followed by SRS	Overall median survival 10 mo post SRS, 15 mo from diagnosis; 26 mo in subgroup with no extra – cranial metastases, neurological deficits and small tumour without necrosis Local control in 85% of lesions, radiation necrosis in 4.4% (1 resection). 19 new metastases developed during observation period. >60% excellent palliation, 275 eventual neurological deterioration Peritumoural edema in 12	Retrospective study
Kim DG et al., 2000 [155] Case series 12/97 – 10/99	N=53 with 121 brain metastases Seoul, S Korea	GK	Median follow up 12 mo, median survival 46 wk 1y actuarial control rate 48% (n=40) ; 6 an 12 mo survival rates 63%, 39%	
Kondziolka et al., 1999 [156] RCT	N= 27 with 2-4 brain metastases , 25mm Pittsburgh, USA	GK + WBRT, n=13 WBRT, n= 14	Rate of local failure 100% WPRT, 8% SRS +WBRT Median time to local failure 6 mo WBRT, 36 mo SRS +WBRT (SS) Median survival 7.5 mo WBRT, 11 mo SRS + WBRT (not SS)	Trial stopped at 60% accrual on interim evaluation Correspondence on this paper [157] is critical of the fact that no functional data are presented. Also note that this study was unable to resolve the question of which approach offers better survival.
Lavine et al., 1999 [158] Consecutive case series 8/94 – 4/97	N=45 metastatic melanoma to the brain Los Angeles, USA	GK (n=33 1 treatment, 11=2,1=3) 5 of 59 procedures salvage for new lesions remote from previous targets, not included in analysis	Mean follow up 12 mo 58% died; actuarial mean survival 43mo from diagnosis, 8mo from SRS 78% improved or stable neurological symptoms for n=32 at 3 mo post SRS, 50% had decreased tumour size, 28% disappearance of lesion, 19% no change, 5% increased	Retrospective data first 16mo, prospective second 16mo.

Table 7: Studies on treatment of brain metastases (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Lederman et al., 2001 [159] Case series, retrospective review of records 1991 - 1999	N=60 with brain metastases from breast carcinoma (1 – 16 lesions) New York, USA	LINAC For n=44, fractionated SRS, 24Gy/ 4 fractions 52 also had WBRT	Overall median survival 15.8 mo after diagnosis, 7.5 mo after SRS. 6,12,24 mo actuarial survival 54.1%, 24.6%, 14.8% For n=44 with FSRS, 9.3% did not complete treatment, died in<1mo. If these excluded, actuarial 6,12,24,36 survival 64.1%,28.2%, 12.8%, 7.7% Median survival in n=15 with single metastasis, 3 with 2 was 11.5 mo post SRS; for n=28 with >2 lesions survival 5.6 mo 1 patient in each group (single 7 fractionated SRS) had radionecrosis	
Li et al., 2000 [160] 6/95 – 7/98 Prospective non-randomised comparison of treatments	N= 70 with newly diagnosed single brain metastasis from lung cancer (SCLC 19, NSCLC 51) Shandong, China	WBRT, n=29 LINAC, n= 23 LINAC + WBRT, n=18	Comparative results for WBRT, SRS, WBRT + SRS: Median survival 5.7, 9.3, 10.6 mo Freedom from local progression: 4.0, 6.9, 8.6 mo Freedom from new metastasis 4,1, 6.7, 8.6 mo Post treatment # with KPS improvement 41.4, 82.6, 88.9% (not SS) Progression of metastasis accounted for 51.7, 50.0, 28.3% of deaths Combined therapy not SS better than SRS except for more favourable freedom from new metastasis	SRS treatment better than WBRT, value of adding WBRT to SRS unclear
Liščák et al., 1997 [161] Case series 1992 - 1996	N= 21 of 25 with brain metastases from breast carcinoma; single metastases in n=15. Prague, Czech Republic	GK Primary treatment in n=17	N= 10 died at mean 7.6 mo (2-16) post SRS, none with local progression. Follow up of other 11 patients 5.9 mo(2-16), I local recurrence. Edema in 2 cases.	

Table 7: Studies on treatment of brain metastases (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Manning et al., 2000 [162] Case series 1996 –1998	N=32 with 57 brain metastases Richmond, USA	FSRT median 27Gy in 3 fractions ; previous surgery in 6.	Actuarial median survival times 14.3, 11.8 and 2.7 mo for patients with RPA class I, II and III respectively. Of n=22 with follow up of 6 mo, 20 had some shrinkage of tumour, 3 of these developed new lesions outside target, 2 developed local progression. N=4 had seizures post FSRT, 2 had radionecrosis	
Maor et al., 2000 [163] Case series, retrospective	N=84 56% with solitary lesion Houston, USA	LINAC; fast neutrons for 3 cases 55% had prior WBRT and/or surgery, 45% SRS first treatment for metastasis,	Median survival post SRS 7mo Median follow up for 17 alive at last follow up 10mo. 1 and 2 y actuarial survival rates 29% and 13% Complete or partial response in 29/39 with solitary met, 14/29 with multiple lesions Clinical symptoms related to metastasis in 76%, symptomatic relief in 64% of these after SRS 46% of patients had subsequent relapses, 23% included in field lesions	Few details re symptomatic relief
Mori et al., 1998 [164] Case series, consecutive cases 1988 - 1996	N= 35 with brain metastasis from renal cell carcinoma Pittsburgh, USA	GK	Median survival 11mo post SRS, 14 mo post diagnosis. I and 2 y actuarial survival rates 43% and 22% Addition of WBRT did not improve survival Local control 90%, evaluated in 26 patients Neurological deficits improved in 5/20	

Table 7: Studies on treatment of brain metastases (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Muacevic et al., 1999 [165] Case control study SRS 12/94 – 7/97 Surgery 8/90 – 7/97	N=108 with small, solitary brain metastases Munich, Germany	GK, n=56 Microsurgery + WBRT, n= 52	Actuarial 1y survival 53% surgery, 43% SRS (not SS). In SRS group Complete response 13%, partial response 43%, stable 39%, progression in 5%. N=4 had 2nd SRS, progression not stopped in 2. Freedom from distant tumour progression at 1y 90% surgery, 75% SRS (not SS). 1y freedom from local recurrence 75% surgery, 83% SRS (not SS) Clinical improvement in 88% surgery, 91% SRS. Similar perioperative morbidity and mortality rates	Conclude that for highly selected patients with single small metastases, SRS alone can achieve control rates as good as surgery +WBRT or SRS +WBRT. Latter conclusion based on proposed approach of MRI follow up and second SRS treatment, rather than on empirical data.
Nakagawa et al., 2000 [166] Case series 1990 – 1997 (Abstract only)	N=51 of 54 with brain metastases, 32 with single metastasis Tokyo, Japan	GK, n=37 as initial treatment for metastasis, SRS + WBRT in 29, surgery in 8.	Median survival 7.4 mo. 5y actuarial survival and local control rates 16% and 52%. Median duration of keeping pretreatment QOL 6.9 mo	
Nicolato et al., 1998 [167] Case series, 2/93 – 12/97	N= 290 with single metastases Verona, Italy	GK,	Mean follow up 10.6mo, for n=190. Median survival 11.6mo, 1y actuarial rate 34%. Functional Independence index 52.3 weeks, Palliative Index 49 weeks	
Noël et al., 2001 [168] Consecutive case series 1/94 – 3/00	N= 54 with 97 metastases who previously received WBRT Paris, France	LINAC. Median interval between WBRT and SRS 9mo(2-70)	Median follow up 9mo(1-57) One and 2y local control rates 91.3% and 84%,(excludes 15 metastases where patients died without follow up exam) Mean survival 7.8 mo. Overall 1, 2 and 3y survival rates 65%, 57%, 28%. 6 deaths from brain metastasis evolution. No major complications	

Table 7: Studies on treatment of brain metastases (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Payne et al, 2000 [169] Consecutive case series 1990 - 1999	N=21 with 37 metastases from renal cell carcinoma Charlottesville, USA	GK	15 deaths at mean of about 12 mo after SRS, 6 alive at mean 29 mo after first treatment No clinical complications associated with SRS In n=12 (23 tumours), 6 tumours disappeared, 16 decreased, I unchanged	Details given of all patients; retrospective analysis
Pirzkall et al., 1998 [170] Case series, comparison of treatments 9/84 – 1/97	N=236 with 311 metastases (1-3/patient, KPS>50) Heidelberg, Germany	LINAC, n= 158 LINAC + WBRT, n= 78	Actuarial 1 and 2y local control rates 92% and 86% for SRS +WBRT, 89% and 72% for SRS only. Actuarial median survival 5.5 mo, 1 and 2y rates 30.4% and 13.9% SRS +WBRT, 19.2% and 8.3% for SRS alone. Suspicion of radiation – induced necrosis in n=4	
Sanghavi et al., 2001 [171] Retrospective analysis of case series from 10 centres, comparison with RTOG data base 1/88 – 5/88	N= 502 with brain metastases 9 centres in USA, 1 in Brazil	LINAC, 6 centres GK , 4 centres All + WBRT	Overall median survival 10.7 mo Median survival for RPA classes I, II and III:16.1, 10.3 and 8.7 mo Comparative values for WBRT only from RTOG data base 7.1, 4.2, 2.3 mo	
Sansur et al., 2000 [172] Case series 7/92 \- 8/97	N=193 with brain metastases (4 or less per case, single in n=106) Baltimore, USA	GK Prior WBRT in 76%, surgery in 21%	Median time between diagnosis and SRS 4.5 mo For n=173 with median follow up 8.5 mo (12 – 100) overall median survival after SRS 7.5mo (4.9 mo for n=75 4.9 mo) For n=134, local control of largest metastasis 82% No change in KPS for n=80 following SRS	

Table 7: Studies on treatment of brain metastases (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Schoeggl et al., 1999 [173] Case series 1/93 – 4/97	N= 97 with multiple brain metastases Vienna, Austria	GK	Median survival 6 mo post SRS, actuarial 1y survival 26%. For those with KPS <70, median survival 1.2 mo, for > 70, 7.8mo. Extracranial metastasis median survival 1.7mo, brain metastases only 9.2 mo. Local control 94%. Clinical response (n=91 – 6 early deaths), 84% improved, 14% stable, 2% declined. Peritumoral edema in 5, radiation necrosis in 1	
Schoggl et al., 1998 [174] Case series 1/93 – 9/95	N= 23 with brain metastases of renal cell carcinoma Vienna, Austria	GK 14 GK only 9 GK + WBRT	Local control rate 96% 1y actuarial survival 48% (KPS <70 1.8 mo, > 70, 13.2 mo) Neurological symptoms improved in n=20, unchanged in 2, worse in 1.	Individual patent details presented. Most of these cases would have been included in the series described in the following two studies.
Schoggl et al., 2000 [175] Retrospective, case control study 8/92 – 10/96	N=133 with single brain metastasis, limited systemic disease Vienna, Austria	GK, n=67 Microsurgery, n= 66 Additional WBRT (30Gy/10d)	Median survival 12mo after SRS, 9 mo after surgery (NSS) 1y actuarial survival SRS 52%, surgery 44% median hospital stay 8d for surgery group, SS longer than SRS group Local control SS better for SRS (95%) than for surgery (83%), but this associated with cases with radio-resistant lesions in the surgery group. NSS difference for 'radiosensitive' lesions NSD in distant recurrence rates For SRS group peritumoral edema in 5, radiation necrosis in 1 111/133 died at median of 7.9 mo (0.3 – 44.3)	As noted by authors, median tumour volume for SRS group was lower than for surgery group (7.8 cm3 v 12.5 cm3), so that there are limitations on the matching of the groups Authors conclude results of the two approaches are comparable, recommend use of SRS where possible, except for large lesions, as it is non invasive and needs shorter hospital stay.

Table 7: Studies on treatment of brain metastases (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Serizawa et al., 2000 [176] Retrospective comparison of treatments from two case series 1990 - 1999	N=96 with brain metastases from NSCLC (up to 10 lesions at initial diagnosis) Chiba, Japan	Surgery for large lesions + GK, n= 62. New lesions with GK Surgery + WBRT, n= 34. New lesions with WBRT Chemotherapy for both groups	Actuarial tumour control rate at 1y, 94.8% for SRS group, Mean survival times 377d in SRS, 199d in WBRT (SS) Neurological survival SS longer in SRS than WBRT (graph, summary data not given) Mean estimated time free from neurologically impaired QOL 737d for SRS, 270d WBRT (SS)	Control rate for WBRT not given
Seung et al., 1998 [177] Case series 1991 - 1995	N=55 with brain metastases from melanoma (140 lesions treated, single lesions in n= 21) San Francisco, USA	GK, initial treatment n=28, n=16 for recurrence after WBRT, 11 as boost to WBRT	Median follow up 75 wk Overall median survival 35 wk post SRS, actuarial survival 58% at 6mo, 34% 1y Survival for single met cases 35wk, multiple mets 33wk (not SS) Overall actuarial FFP rate (n=46, 113 lesions) 89% at 6mo, 77% at 1y N=4 acute and n=5 late RTOG >2 morbidity	
Shirato et al., 1997 [178] Case series 9/90 – 3/94	N = 44 with single brain metatasis Sapporo, Japan	LINAC, n= 39; FSRT, n=5 (for larger / inoperable lesions)	Overall median survival time 261d, actuarial survival 1y 34%, 2y 9% Initial response rate 92% (34% complete contrast disappearance on imaging) Neurological improvement in 76% of n= 33 in 3mo Crude local control rate 84%, actuarial rates 93% at 6mo, 66% at 12 mo 48% needed salvage treatment for relapse, 7 of these with WBRT no further treatment, of 14 SRS only , 5 needed retreatment . Late radiation damage observed with retreatment.	

Table 7: Studies on treatment of brain metastases (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Sneed et al., 1999 [179] Retrospective comparison of treatments from case series 1991 – 2/97	N=103 with newly diagnosed brain metastases (50 with single lesions) San Francisco, USA	GK, n=62 GK + WBRT, n=43	Survival and local FFP same for both treatments (11.3 v 11.1 mo and 71% v 79% at 1y) Brain FFP SS worse for RS than SRS + WBRT (28% v 69 at 1y), however allowing for salvage therapy of first failure 1y control rates were 62% and 73%, not SS.	Excluded 26 cases, different treatments etc As noted by the authors, QOL data not available for these patients More patients with multiple metastases in SRS +WBRT group (67% v 42% for SRS)
Suzuki et al., 2000 [180] Case series 7/98 – 1/00	N=24 with 10 or more brain metastases Fukuoka, Japan	GK	Mean follow up 13.2wk, 50% died. Actuarial survival 49.3% at 24wk, 12.3% 36wk KPS improved in 6/12 symptomatic patients, unchanged in 5, worse in 1	Authors note low morbidity and good QOL
Tokuuye et al., 1998 [181] Case series 7/91 – 3/97	N=64 with 95 metastatic brain tumours Tsukuba, Japan	FSRT, 42Gy in 7 fractions except melanoma 48 Gy in 8 fractions	Overall median survival 8.3 mo, 1y actuarial tumour control rate 91%, survival rate 33%	Paper also considered treatment of 10 patients with primary brain tumours

Brain tumours

SRS treatment of primary brain tumours, other than acoustic neuromas, was not specifically considered in the 1998 AHFMR report. In the present report, separate classification has been made for studies on treatment of meningionas and pituitary tumours. Studies on other types of brain tumour, primarily malignant lesions, are summarised in Table 8. It is of interest that in the eight studies that used linear accelerator technology, four used fractionated doses. One of these compared LINAC with FSRT and concluded that they were equally effective but that use of FSRT was associated with a lower rate of complications. In the remaining papers, any comparisons with surgical and other radiotherapy approaches were based on literature reports from other centres or historical controls. There were six studies that used the GK, one of these in association with a brachytherapy technique.

Five studies reported treatment of gliomas, indicating relatively limited success. Abdelaziz [182] comments that unsatisfactory results of SRS for GBM and fair results for astrocytomas reflect use of a highly focal treatment for the management of diffuse, infiltrative disease. However, Alexander and Loeffler [183] suggest that SRS can result in significantly improved survival and should be considered for patients with small, radiographically distinct and focally recurrent GBM. The need for appropriate use with surgery and other adjuvant therapy is also noted.

Two of the studies considered treatment of children and indicated useful results for some types of brain tumour.

Nieder et al. [184] have published a review of treatment results for recurrent malignant gliomas. They conclude that post - operative chemotherapy and radiotherapy appear equally effective, but with differing toxicity profiles; survival results of various radiotherapy methods are largely comparable, with a trend to improved results with combined radiotherapy and chemotherapy; and that considerable toxicity is associated with radiosurgery or brachytherapy.

Irish et al. [185], from analysis of cases in a clinical/ imaging data base, have suggested that there is evidence for selection bias in uncontrolled trials of SRS. Those patients with malignant glioma deemed eligible for adjuvant SRS had more favourable prognostic factors and significantly longer median survival than ineligible patients. SRS – eligible, conventionally – treated patients with GBM and a group of SRS –treated patients had similar median survival times (16.4 v 19.7mo). Irish et al. suggest that a phase III study of SRS for malignant glioma would be unlikely to yield a positive result and may not be necessary.

Table 8: Studies on SRS treatment of brain tumours

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Alleyne et al., 1997 [136] Case series	N=24 with malignant gliomas Atlanta, USA	LINAC with patient rotator Prior XRT in 14, surgery in 8	Clinical complete or partial response in 5%, stable in 45%, progressive disease in 50%. Median survival time 38 mo	Preliminary results, part of study that considered other conditions
Cho et al, 1999 [139] Cohort study 4/91 – 1/98	N=71 with recurrent high grade gliomas Minneapolis, USA	LINAC SRS, n=46, median MPD 17Gy FSRT, n=25; median 60Gy, 33 fractions (FSRT group had larger tumours(>4cm, n=20) or tumours close to eloquent structures)	Actuarial median survival 11 mo for SRS, 12 mo for FSRT Late complications 30% of SRS, 8% of FSRT	Retrospective data Suggest SRS and FSRT equally effective, though note SRS group has better pre - treatment prognosis, but FSRT has lower risk of late complications
Chung W-Y et al., 2000 [186] Consecutive case series 3/93 – 12/99	N=31 with craniopharyngiomas Taipei, Taiwan	GK; initial treatment in 6, for recurrent tumours in 25. Surgery prior to SRS achieved total excision in 4, partial excision in 19.	MRI findings indicated complete response in 32.3%, partial in 32.3%, no change in 22.6%, volume increase in 12.8% Clinical outcomes were excellent in 29%, good in 39%, fair in 26% and poor in 6%	Details of responses to signs and symptoms provided Authors suggest multimodality management of craniopharyngiomas provides better quality of survival and long term tumour control; SRS and adjuvant stereotactic procedures an alternative to microsurgery for recurrent/residual tumours
Debus et al., 2000 [187] Prospective case series 1990 –1997	N= 37 with skull base chordoma (a) , n=8 condrosarcoma (b) Heidelberg, Germany	FSRT	Actuarial local control for (a) 82% 2y, 50% 5y, survival 97% 2y, 82% 5y All (b) Maintained local control, survival to 5y	
Hodgson et al., [188] Case series 12/87 – 12 /97	N=62 recurrent, n= 28 residual brain tumours in children Boston, USA	LINAC	Median follow up 24 mo post SRS, 55.5 mo for n=34 still alive Median progression free survival 13mo 3y actuarial risk of reoperation 37%; 3y risk of radionecrosis 26%	Details of patients alive free of progression. Includes further details of rates for different types of tumour.
Hudes et al., 1999 [189] Case series 11/94 – 9/96	N= 19 with GBM, 1 with astrocytoma	FSRT, as salvage XRT post op for all cases	Median survival 10.5 mo, 1y actuarial rate 20% Decreased steroid requirements in 60% No major toxicity experienced	Phase 1 dose escalation study

Table 8: Studies on SRS treatment of brain tumours (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Jawarhar et al., 1999 [190] Case series 1987-98	N=22 with progressive anaplastic ependymoma Pittsburgh, USA	GK, 19 had XRT prior to SRS, 50% chemotherapy before or after	Median follow up 21 mo (4-84) in n= 21 Reduction or stabilisation of tumour in 68% Median actuarial survival from diagnosis 10.1y and from SRS 2.2y	SRS suggested as safe and effective as a salvage adjuvant therapy
Jawahar et al, 2000 [191] Case series over 11 y period	N=27 with 29 hemangioblastomas (benign) Pittsburgh and Rochester, MN, USA	GK All had prior surgery	Mean follow up 4y Median survival after SRS 6.5y and from diagnosis 15y Actuarial 2y rate of freedom from progression 84.5%, 5y 75.2%	
Kida et al., 2000 [192] Case series	N=51 with low grade astrocytomas Komaki City, Japan	GK	N=12 Grade I – mean follow up 24.8 mo, 6 tumour regression, 5 minor or no change, I progressed. N=39 Grade II: mean follow up 28.5 mo, 18 tumour regression, 16 minor or no change, 5 progressed. Radiation – induced edema in 35.3%	
Kobayashi et al., 2001 [193] Case series 1991 – 2000	N=33 with pineal and related tumours. Komaki City, Japan	GK Prior surgery in n=10, XRT in 8, cisplatin/ etoposide in 10	Mean follow up of 23.3 mo (6-81) for 30 of 33 cases. Complete response 26.7%, partial response 42.4%, progression in 26.7% 100% control for 7 germinomas and 3 pineocytomas	

Table 8: Studies on SRS treatment of brain tumours (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Kondziolka et al., 1997 [194] Case series 1987 –1995	N= 64 with GBM, n=43 with anaplastic astrocytomas (AA) Pittsburgh, USA	GK GBM group 41 resections, 23 biopsies , 45 treated with SRS before disease progression Carmustine/ cisplatin in n=47 AA group resections in 19, biopsies in 24, 47% SRS before disease progression	GBM group. Median survival after SRS 16 mo (1-74), 30 mo(2-74) when SRS at time of tumour progression. Actuarial 2y survival 53%. 75% needed no further surgical procedures AA group: Median survival after SRS 21 mo, 31 mo (3-47) for those receiving SRS at time of disease progression. 72% needed no further surgical procedures No survival difference for those receiving chemotherapy for either group. Compared to RTOG median survival values, lower survival for grades I and II, higher for III - VI	Reference to improved survival compared to historical controls; apparently refer to studies at other centres with varied patient populations and approaches.
Lederman et al., 2000 [195] Case series 9/94 –12/97	N= 88 with GBM and recurrent tumour 59 prior extensive resection, 17 limited resection Median KPS 70(50-100) New York, USA	FSRS, 60 Gy in 33 fractions Paclitaxel weekly , median 120 mg/m2, immediately preceding SRS	Median survival from diagnosis 15mo (4.4-77); from SRS 7.0 mo, 1 and 2 y survival 17% and 3.4% 7% had stable decrease in tumour, median survival 14 mo, similar volume in 33%, survival median 8.3 mo, increase in 49%, median survival 8.8mo. Out of field recurrence in 8%, survival 8.8 mo No SS difference in survival between those with low and high KPS scores	
Miller et al., 1997 [196] Consecutive case series 1/90 – 12/95	N=32 with 35 malignant skull base tumours Davis, USA	GK N=15 prior XRT, 12 XRT post SRS	Median follow up 2.3y (0.2 – 6.1) Complete regression 22%, partial 28%, no change 41%, progression 9% Actuarial survival 82% 1y, 76% 2 y , 72% 3y 1 radiation induced optic neuropathy	

Table 8: Studies on SRS treatment of brain tumours (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Raco et al., 2000 [197] Case series of different tumours 1987 – 1995	N= 114 children with benign and malignant brain tumours. Rome, Italy	LINAC SRS as part of primary treatment in n=35	Considerable detail on survival, tumour size etc. results include: Glioma: n=65, 35% deaths, 36% controlled or disappeared; embryonal and ependymal tumours: n=20, 55% and 20% pineal tumours: n= 21, 48%, 48% craniopharyngiomas: n=8, 13% , 50%	Authors consider results for glial tumours encouraging, SRS should be primary treatment for pineal and diffuse brain stem tumours, less useful for embryonal and ependymal tumours
Shrieve et al., 1999 [198] Case series 6/88 – 1/9	N= 78 with GBM Boston, USA	LINAC All had previous surgery or biopsy	Median actuarial survival from diagnosis 19.9 mo, 1y and 2y survival 88.5%, 35.9% 50% had surgery following SRS (median 7.9 mo post SRS) For n=65 deaths, local treatment failure in 38%, 40% failure marginally beyond treated volume, 10% failure beyond 5 cm of treated volume, 12% no evidence of recurrence For n=13 alive at 2y, KPS declined from mean 91.5 at diagnosis to 87 No new neuropathies secondary to SRS	
Yu et al., 2000 [199] Case series 10/96 –6/99	N=46 with craniopharyngioma Beijing, China	GK + brachytherapy with ^{32}P solution	Mean follow up 16 mo (6-24) Overall tumour control rate 90%	

Meningioma

Studies that considered use of SRS for treating meningiomas are listed in Table 9. All were case series, with some also giving details of cases treated by microsurgery.

Fifteen of the studies used the GK, 6 LINAC and 3 FSRT. In addition, a study that used fractionated XRT is included as this was intended to provide some comparison with SRS.

These papers give indications of benefits to patients through a proportion of those treated having tumour control and improvement of neurological symptoms. Two of the studies included patient surveys, which indicated high satisfaction with SRS.

As with other applications of SRS, a variety of populations and clinical situations are described. It is not possible from these studies to obtain any realistic comparison between different types of SRS or between SRS and other types of treatment. The use of FSRT is of interest, but the three studies concerned give only preliminary outcomes.

A retrospective UK study [200] on efficacy of conventional radiotherapy for benign skull base meningioma in 82 patients (1962 to 1992) found 5 and 10 year progression free survival rates of 92% and 83% and an overall 10 year survival rate of 71%. The authors point to the excellent long term control and survival as being a baseline for evaluation of SRS and other newer treatments. A paper by Condra et al. [201] considered long term outcomes for 262 patients with benign meningiomas, 229 treated by surgery alone, 21 with surgery plus radiotherapy and the remainder with radiotherapy or SRS only. Actuarial local control at 15y was 76% for those who had had total excision and 87% for those with selective excision followed by radiotherapy. Selective excision alone was inadequate therapy.

Table 9: Studies on treatment of meningiomas

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Aichholzer et al., 2000 [202] Case series 09/92 –10/95	N=46 81% benign tumours, 13% atypical, 6% malignant Vienna, Austria	GK; 31 had had previous surgery, 3 fractionated XRT	Decrease in tumour diameter 58%, no change 44%, increase 4%. Neurological symptoms: no change 58%, better 33%, worse 9%. Overall 47% improvement for group treated with SRS only, 26% in others. Tumour recurrence in 2 after SRS	Authors note that total resection is the standard aim – preferred with the hemispheres but skull base lesions present difficulties Note that long term follow up is needed to establish efficacy
Alheit et al., 1999 [203] Case series 7/93 – 11/97	N= 21 with skull base n=3 with upper skull meningiomas Sutton, UK	FSRT; 50 –55 Gy, 30 –33 daily fractions N==11 as primary treatment, 10 first recurrence, 3 second recurrence	Median follow up 13 mo Progression free survival at 1y 100%	Suggest that many of tumours in this series had size and location that would not be amenable to safe SRS.
Black et al., 2001 [204] Prospective case series 1987 - 1994	Skull base meningioma N=100 in care of one neurosurgeon Boston, USA	Observation 15%, surgery 45%, radiation 13%, surgery + radiation 27%, radiation only 13% SRS using LINAC; patients with tumour size >3cm diameter or within 5mm of optic chiasm treated with conformal fractionated radiotherapy (54Gy over 6 weeks). Median follow up 5 years	Complete surgical removal in 47%, greater than 50% in 93% No mortality, 5 patients with complications following surgery, one long term complication of SRS . One tumour progression in 5 years	No clear comparison of results from surgery and SRS
Chang SD et al., 1997 [205] Case series, 1989-96	Cranial base meningiomas N=55, 38 with previous surgery Stanford, USA	LINAC	Mean follow up 48.4 mo (17-81) 27% reported improvement, 62% no change, 5% worse. Complete resolution of cranial nerve deficits in 42% (8 of 19)	Note limited follow up

Table 9: Studies on treatment of meningiomas (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Chang SD et al., 1998 [206] Retrospective case series	Cavernous sinus meningioma N=24, 16 with prior surgery Stanford, CA, USA	LINAC. 14 – 20 Gy	Mean follow up 45.6 mo (19-80) Tumour control in 63%, shrinkage in 37%, none of larger tumours >12 mL decreased Neurological status improved in 42%, unchanged in 50%. Complete resolution of cranial nerve deficits in 69%.	Authors note relatively short follow up. Results said to be comparable to GK and to compare very favorably with microsurgery , though no data to support these points.
Debus et al., 2000 [207] Case series 1989 -1998	N=55 with benign skull base meningioma, all considered inoperable Heidelberg, Germany	FSRT; median daily fraction size 1.8Gy, 5 times per week. Median prescribed total dose 56.6 Gy	Median follow up 60 mo (19 mo-11y) Overall actuarial survival 97.5%, progression – free survival 95% No brainstem toxicity or optic neuropathy	Preliminary account; relatively limited details of follow up data Assess risk of inappropriate stereotactic irradiation when no prior histological verification as < 2%
Hakim et al., 1998 [208] Case series Retrospective analysis 10/88 – 12/95.	127 patients with 155 meningiomas Boston, USA	LINAC, 88 – 92 on modified 6MV, subsequently on dedicated LINAC. Median dose 15 Gy 48 with SRS as initial treatment. 80 with regrowth and 27 with persistent disease had SRS after at least one of surgery, XRT, I-125 implant, p beam, hormone, chemo	Median follow up 31 mo Freedom from progression in 84% patients at 22.9 mo (1.2 –79.8); 16% showed progression of disease. Actuarial control for patients with benign tumours 89.3% at 5 years Median times to freedom from progression for benign, atypical and malignant tumours was 20.9, 24.4 and 13.9 mo Six patients, 4.7% permanent SRS – related complications	Individual patient details given for cases where there was recurrence. Comments on this paper note diversity of lesions treated Commentators on paper accept that microsurgery is the preferred approach for meningiomas but note lack of clear criteria for when SRS should be used.
Hudgins et al., 1996 [209] Case series	N=100 consecutive patients with meningioma; 91 had residual tumour following surgery Dallas , USA	GK,	8% patients improved, 74% unchanged, 12% worse, 6% died (5 due to tumour – related causes). No tumour growth, permanent complications in 96% of 77 patients with tumours ,< 3.1 cm in diameter . Time of follow up not clear.	Variable imaging follow up. Limited details of clinical measures

Table 9: Studies on treatment of meningiomas (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Iwai et al., 1999 [210] 1994 –1996 Case series	N=24 with skull base meningiomas. Previous surgery in 8. Osaka, Japan	GK.	Median follow up 17.1 mo, 100% tumour control. 50% unchanged clinically, 46% improved	Comparison made by authors with various papers reporting surgical results. Commentary on paper notes not possible to draw definite conclusions on efficacy from this study (etc)
Iwai et al., 2000 [211] Case series 1994 – 1998 (Abstract only)	N=77 with skull based meningioma Osaka, Japan	GK	Mean follow up 26 mo (6-60) Tumour control 96% (68% tumour decreased) Clinically, 30% improved, 64% no change In survey of 50 patients, 68% felt they had clinical improvement , 4% that they had deteriorated. 58 patients (79%) able to continue their previous work	Continuation of series reported in earlier paper
Kondziolka et al., 1999 [7] Consecutive case series 1987 - 1992	N=99 with meningioma Pittsburgh, USA	GK; prior surgery in 57%	No further surgery required in 93% Majority of meningiomas decreased in size, but limited numbers of cases available for follow up. 63% of 97 tumours became smaller (eg 10/17 at 2-4 y; 19/26 at 6-8y) , 5% increased Actuarial worsened neurological rate 8.8% at 38 –120 mo (4.9% radiation – related) Survey results from 70/89 patients or their relatives 5-10y post SRS. SRS described as successful by 96%, 97% would recommend to family/friend	

Table 9: Studies on treatment of meningiomas (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Lesniak and Williams, 1999 [212] Consecutive case series	N=50 with meningioma, 36 benign, 14 atypical/ malignant Baltimore, USA	LINAC (FSRT) (following failure of surgery and /or XRT) administered in 7 fractions	Mean follow up 17.9 mo (0.5 – 92 mo), 14.4 mo benign, 26.5 mo malignant I patient had radiologic progression. Others unchanged of smaller tumour size (no details given) No complications of treatment observed.	Limited clinical outcome detail provided.
Liščák et al., 1999 [213] Case series 1992 –1998	N=67 with cavernous sinus meningioma Prague, Czech Republic	GK; primary treatment 64%, prior surgery in 36%	Follow up median 19mo (2-60) for n=53 (52 with radiology) Tumour volume decreased in 52%, no change in 48%. Clinical symptoms improved in 36%, no change 60%, worse 4%	
Maguire et al., 1999 [214] Case series 7/85 – 1/98	N=28 with cavernous sinus meningioma Durham, USA	Fractionated XRT; for n=20,	Actuarial 8y overall survival 96%; actuarial 4y and 8y progression free survival 92% and 81%	Treatment conditions with the LINAC were not the same for all 28 patients Authors discuss comparison with SRS, suggest this limited to relatively small lesions at a distance from optic chiasm.
Muthukumar et al., 1998 [215] Case series	Tentorial meningiomas N=41 Pittsburgh, USA	GK, N=18 had had an average of1.9 previous surgical procedures, 2 had prior XRT	Mean follow up 3y 19/41 improved neurological symptoms, 20 no worse, 2 continued facial pain Reduction in tumour volume in 44%, no growth in 54%, increase in 2%	
Nicolato et al., 1996 [216] Case series 2/93 – 9/95	N=97 with skull base meningioma, report describes 50 cases Verona, Italy	GK, mean 25.4 Gy, 22 primary treatment	Mean follow up 14mo (4-31) Actuarial 1 and 2 y growth control rates 97% and 100% 6% had signs of neurological worsening	
Ojeman et al., 2000 [217] Case series 1/91 –5/99 Retrospective study	Malignant meningioma N=22 San Francisco and New York, USA	GK, 3 as boost to XRT, 19 for recurrence	Mean follow up 30 mo Actuarial 2 and 5 y survival 75% and 40%; progression free survival 32% and 26% Radiation necrosis in 5/22	Authors note difficulty associated with changing criteria for diagnosis over past 15 y; efficacy of SRS relative to other therapies will require further evaluation.

Table 9: Studies on treatment of meningiomas (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Pendl et al., 1998 [218] Case series 4/92 –12/95	N=43 with cavernous sinus meningiomas Graz, Austria	GK, 17 as primary treatment N=24 surgery +SRS N=2 Surgery	Mean follow up 39 mo (18-62) Tumour disappearance in I case, reduction of volume in 35%, stable in 63% Improvement of cranial nerve deficits (94 prior to SRS, 55 after) . No radiation – related complications.	
Pendl et al., 2001 [219] Case series 4/92 – 5/98	N=197 with skull base meningiomas Graz, Austria	GK; primary treatment for n=105, combined surgery and SRS for n=92	Mean follow up 55 mo post SRS (24-97); n=33 lost to follow up. Tumour volume decreased in 51%, no change 47%, small increase 2%. Neurological status stable in 61%, better in 35%, worse in 4%.	Brief details given. No separate data for primary SRS treatment cases vs SRS + surgery.
Roche et al., 2000 [220] Consecutive case series 1992 -1998	N= 80 with cavernous sinus meningioma Marseille, France	GK, primary treatment in 50, adjuvant to surgery in 30	Median follow up 30.5 mo (12-79) 5y actuarial progression free survival 92.8% Of n=54 with oculomotor deficits, 8 recovered, 15 improved, 1 worse, n=13 with TGN 3 recovered, 4 improved, 1 worse. 2 long term neurological deficits.	Draw attention to absence of complications and tumour growth following change in treatment planning, though this would be applicable to a small number in this series
Shafron et al., 1999 [221] Case series 1/89 – 7/97	N=70 with 76 benign meningiomas Gainesville, USA	LINAC	Local control rate 100% N=50 had follow up of > 1y; neurological condition better in 3, worse in 1, unchanged in 46. For n=44, with 48 tumours, on radiological follow up 44% were smaller, 56% unchanged.	Limited detail on follow up.
Shin et al., 2001 [222] Case series, retrospective 6/90 – 6/99	N=40 with cavernous sinus meningiomas Tokyo, Japan	GK	Median follow up 42 mo (12 –123) Actuarial tumour control rates 86.4% 3y, 82.3% 10 y. No recurrence for cases where all tumour had been irradiated, 100% in 3 with larger tumours and only partial coverage.	

Table 9: Studies on treatment of meningiomas (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Stafford et al., 2001 [223] Consecutive case series 1990 – 1998	N=190 with 206 meningiomas, 178 with single tumour Rochester, MN, USA	GK 112 prior surgery 16 prior XRT	Median follow up 40 mo (2-109) for n=189 7 deaths from tumour progression, 1 from hemorrhage, 14 unrelated. 5 and 7y cause- specific survival rates 94% and 92%, overall survival 82%. Tumour control rate 91%; 93% for benign tumours, 68% for atypical, 0 for malignant. N=15 new cranial neuropathy, 4 of which resolved.	
Subach et al., 1998 [224] Case series 9/87 – 4/95	N=62 with petroclival meningioma Pittsburgh, USA	GK Previous surgery for n=39	Mean follow up 42 mo (12-101) 2 unrelated deaths Clinical improvement 21%, stable 66%, neurological deterioration 13% (5/8 with tumour progression) Tumour control rate 86.7%; higher for patients without prior XRT but not SS	
Villavicencio et al., 2001 [225] Case series 10/88 – 5/94	N=56 with skull base meningiomas Boston, USA	LINAC N=36 prior surgery, n=7 XRT	Median follow up 26mo(6-66) Actuarial tumour control rate 95%; 44% had decreased tumour volumes, 5% had increased in size. At median 28 mo, 34% had improved clinically, 9% worsened, 57% unchanged. N=3 recurrent tumour 5 (9%) long term complications	

Pituitary tumours

Table 10 lists studies that considered the use of SRS in treatment of pituitary tumours. Twelve of these used GK and three linear accelerator technology. One study compared LINAC and FSRT approaches, and recommended FSRT in view of relatively high morbidity in patients treated with SRS.

The remaining studies were all case series. One of these considered FSRT, suggesting this was safe and effective but that SRS might have an advantage because of faster reduction in overproduction of hormones by active tumours. Further work appears necessary to establish the place of FSRT in this application.

A number of the studies indicated good rates of tumour control and of normalization of hormonal levels. One series with long term follow up indicated the potential for delayed complications.

Other tumours

Table 11 lists six other studies that considered use of SRS in the treatment of nasopharyngeal cancer and uveal melanoma. All were case series.

Table 10: Studies on SRS treatment of pituitary tumours

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Höybye et al., 2001 [226] Case series 1975 -1987	N=89 with ACTH-producing adenomas, 18 available for detailed follow up Stockholm, Sweden	GK, 60-240 Gy, primary therapy in 15,	Of 18 patients 83% cured (ACTH secretion) , no recurrence at mean follow up of 17y (12 –22) 11/16 developed hypothyroidism GH insufficiency in all 13 who were evaluated No damage to optic nerve	Authors note series treated before availability of modern imaging methods, suggest prospective study using current technology Point out that new pituitary insufficiencies may occur> 10y after treatment.
Inoue et al., 1999 [227] Case series From 1991	N=122 with pituitary adenomas Gunma, Japan	GK, N=63, N=35 followed up for > 2y. most as second treatment for residual or recurrent tumours (17 functioning) 3 with relatively large tumours had surgery post SRS Microsurgery: n=59 (66 resections) most as primary treatment. 18 with post op SRS. 31 functioning adenomas	SRS: 18 tumours shrank, 15 unchanged, 2 increased 11/17 showed normal hormone values post SRS Surgery: Total tumour removal in 54.2%, normalisation of hormonal values in 77.4% of functioning tumour cases. 7 of SRS cases followed for >2y, decrease in tumour size for 6 of these.	Authors note effect of SRS on ACTH levels was gradual
Izawa et al., 2000 [228] Treatment since 1993	N=74 with follow up of >6mo; Tokyo, Japan	GK, n =40 SRS following surgery	Mean follow up 27.8 mo. Tumour control on 93.6%; shrinkage in 24.1% (26.1% NFA, 23.2% FA); Endocrinological improvement in 80.3% of FA	Follow up to 1999 report by Hayashi et al. at earlier stage in this series.
Landolt and Lomax, 2000 [229] Case series	N= 20 with prolactinomas Zurich, Switzerland	GK, with dopamine agonist treatment at time of SRS in n=9.	N=5 successful, normal prolactin in 5-41 months, n=11 improved, n=4 failed	
Lim et al., 1997 [230] Case series 3/92 – 3/96	N=65 with pituitary adenomas (43 active, 22 non-functioning). Seoul, South Korea	GK 33 recurrent/residual following surgery	Mean follow up 26.3% (6-54 mo) Improvement in 78% prolactinoma, 81% acromegaly, 75% Cushings Follow up MRI in 40/65 Tumour control rate 92.5%	

Table 10: Studies on SRS treatment of pituitary tumours (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Martinez et al., 1998 [231] Case series	N=30 with pituitary tumours Madrid, Spain	GK	Follow up 26 –45 mo Reduction in volume or cessation of growth for all tumours. Normalization of ACTH in n= 3 with Cushing's disease N=5 prolactinomas reduction of prolactin levels but normalization did not occur 6/7 with acromegaly showed normalization of growth hormone	Conclude that GK radiosurgery in pituitary tumours is an effective alternative to transsphenoidal microsurgery when compression of surrounding structures does not exist, and that it can efficiently replace conventional irradiation
Milker-Zabel et al., 2001 [232] Case series 1989 - 1998	N=68 with pituitary adenomas 926 functional tumours) Heidelberg, Germany	FSRT, N= 63 LINAC, N= 5	Tumour size: Mean follow up FSRT 38.7 mo (n=60), SRS 46 mo FSRT: unchanged size 68%, partial response 30%, n=1 progression, n=1 unrelated death. For SRS 4/5 reduction, 1 stable Functional response 5y actuarial control rate 93% for FSRT. Normalization in 4/5 SRS	Comparison with SRS not realistic, given numbers. Authors suggest FSRT is effective and safe in this application, though in discussion note disadvantage of delayed reduction in hormone overproduction and suggest SRS might have an advantage .
Mitsumori et al., 1998 [233] Cohort study, comparison of treatments 9/89 – 11/95	N=48 with pituitary tumours Boston, USA	LINAC: n=18 FSRT: n= 30 Prior surgery in n=42	Median follow up SRS 47mo, FSRT 34 mo 3y survival rates SRS 84.4%, 100% FSRT (not SS) 3y tumour control rates SRS 100%, FSRT 91.1% (not SS) Hormonal normalization response to radiation: 3/6 SRS, 8/13 FSRT; normalization: 2/6 SRS, 7/13 FSRT Time to normalization 8.5 mo SRS, 18 mo FSRT	Recommend FSRT where possible, given relatively high morbidity in SRS group (3y rate of freedom from CNS adverse effects 72.2% for SRS, 100% FSRT)

Table 10: Studies on SRS treatment of pituitary tumours (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Mokry et al., 1999 [234] consecutive case series Since 4/92	N=73 with pituitary adenomas, 31 hormonally inactive, 21 prolactin secreting, 16 growth hormone secreting. Graz, Austria	GK, 70 post op and 3 as primary treatment. Mean time after surgery 42.5mo (0-75.4).	Tumour control in 98.3% of 58/77 patients (79%) who were followed up, mean 28.9 mo (3-81) Improvement of pituitary insufficiency in 9.6% and deterioration in 19.2%. Visual function unchanged in all patients For hormonally active tumours, endocrinological cure rate was 57%	SRS considered a useful adjunct following failed pituitary surgery.
Morange-Ramos, 1998 [235] Case series	N=25 with secreting pituitary adenomas Marseilles, France	GK	Follow up 6-36mo In n=15 with acromegaly decrease of 65% in mean GH levels after 6 mo, 77% at 12 mo; only 3/15 considered to be in remission decrease of 46% and 64% in prolactin at 6 and 12 mo in 4 with prolactinomas, but no normalization; normalization of Urinary Free Cortisol in 4/6 with Cushing's disease within 6-12 mo	
Pan et al., 1998 [236] Case series 10/93 – 10/94	N= 73 with pituitary adenomas (50 with active tumours) Shanghai, China	GK	Follow up of n=65 for mean of 29 mo (26 –37) Tumour size: for n=48 secreting tumours, decrease in 54%, stable in 44%, growth in 4%. Corresponding for n= 17 non-secreting, 6%, 88%, 6% Hormones: PRL –reduced for 59%, normal 30% other types reduced 5%, normal 95%	

Table 10: Studies on SRS treatment of pituitary tumours (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Pan et al., 2000 [237] Case series 1993 - 1997	N= 164 with prolactinomas Shanghai, China	GK	Mean follow up 33.2 mo (6-72) for n=128 Tumour shrinkage in 58%, no change in 41%, 2 cases with enlargement. For n=77 with follow up >2y and no bromocryptine, PRL serum levels normalized in 21%, declined but higher than normal in 36%, 8% normalized but became abnormal again For all n=108 followed for>2y, 29% had no improvement in PRL levels	High proportion not followed up. Incomplete data on hormonal levels
Sheehan et al., 2000 [238] Case series, retrospective data 1/90 – 7/98	N= 43 with Cushing's disease Charlottesville, USA	GK All cases had had unsuccessful prior surgery	Mean follow up 39.1 mo (18 –113) Normalization of cortisol levels in 63% at median of 7 mo after SRS. N=3 had recurrence following remission. Tumour volume in N=33: 73% with decrease, 27% no change	
Yoon et al., 1998 [239] Case series, some comparison with earlier series treated with XRT 7/88 – 3/96	N=24 with pituitary macroadenomas Seoul, S. Korea	LINAC	Mean follow up 49.2 m0 (13 –89) 79.2% had normal or improved visual acuity Prolactinomas: 11/13 had normal PRL levels within 1y (compared with 2y for XRT). 12/13 Complete response in 23%, decrease in size in 54%, no change 15% For 8 non-functioning tumours, proportions 12.5%, 37.5%, 50%, and 12.5% progressed	Essentiality feasibility study

Table 10: Studies on SRS treatment of pituitary tumours (cont'd)

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Zhang et al., 2000 [240] Case series 1993 - 1997	N= 79 with growth hormone –producing pituitary adenomas Shanghai, China	GK N=68 treated with SRS as primary procedure 11 had previous surgery	Mean follow up for n=68 of 34 mo(6-52) Normalization of GH levels in 40% at >1y, 96% at >2y Normoglycemia in 57% of n=21 with hyperglycemia Tumour shrank in 52% of N=58 at >1Y, 87% N=45 at 2Y, 92% OF N=26 at 3y	

Table 11: SRS treatment of other tumours

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Chang SD et al., 1999 [241] Case series	Nasopharyngeal cancer N=23 Stanford, USA	LINAC as radiation boost to XRT. N=15 also received cis platinum chemotherapy and XRT	Mean follow up 21 mo (2-64) Local control achieved in all cases, no local recurrences. 35% of cases developed regional or distant metastases. Trend to better survival in the chemo group.	Authors refer to use of brachytherapy for local control
Langman et al., 2000 [242] Case series 6/92 – 12/98	N= 60 with uveal melanoma Graz, Austria	GK	Follow up 15 – 94 mo Tumour regression in 93%; 4 recurrences Neovascular glaucoma developed in 35% , optic neuropathy in 20%	Authors note dose of 70Gy was reduced for later patients in the series, said to have reduced the rate of glaucoma
Marchini et al., 1996 [243] 3/93 – 9/95 Cae series	N=36 with uveal melanoma Verona, Italy	GK, (a) max 81Gy; (b) max 76 Gy; (c) max 72Gy	(a) tumour regression in 9/10, mean follow up 24mo; n=5 with complications (b) local control, 9/9, follow up 16 mo (c) mean follow up 6mo, regression in 7/17, 1 severe complication	Comparable levels of local tumour control may be obtainable using lower doses which authors hope would reduce the rate of complications.
Mueller et al., 2000 [244] 1996 - 1999 Prospective case series (Abstract)	N=35 0f 55 with unilateral uveal melanomas with Follow up > 1y Munich, Germany	GK	Local control in 97% The median visual acuity decreased from 20/60 to 20/200 at 1y	
Tate et al., 1999 [245] Case series 10/92 – 5/98	N=23 with nasopharyngeal carcinoma Stanford, USA	LINAC as boost to prior XRT (<4wk) N=15 cis platinum	Mean follow up 21 mo (2-64) No local recurrence. 3y actuarial relapse- free rate 37.5% for SRS group, 59% for SRS + cis platinum 2 cervical lymph node recurrence. All n=7 with WHO 1 and 2 tumour subtypes developed distant metastases (4 deaths). For n=15 with WHO 3 neoplasms, 2 recurrences	

Table 11: SRS treatment of other tumours (cont'd)

Authors, study design	Patients/Condition	Intervention	Outcomes	Comments
Zehetemayer et al., 1998 [246] Two case series with different SRS methods 10/93 –2/98	N=82 with uveal melanoma Vienna, Austria	GK, n=62 (7 with 1 fraction, 41 with 2, 14 with 3) LINAC, n=20 (5 – 7 fractions)	For GK: mean follow up 28mo Tumour control rate 98% (not stopped in 1 eye); recurrence in 1 eye. 54 eyes could be preserved. 37% cataract, 29% uveitis,19% glaucoma, 2% retinopathy, 26% optic neuropathy, 8 metastatic disease (6 deaths) For LINAC: Local control in 11/12 with follow up >3 mo. No intraocular side effects, mild sub-acute side effects on lids and conjunctiva	Note posterior segment complications associated with dose/ fraction. Anterior segment complications related to initial tumour volume. Preliminary results only for LINAC

Parkinson's Disease

In a general review on surgery for Parkinson's Disease, Rosenfeld [247] notes the need for caution in use of SRS because of the lack of physiologic guidance and confirmation of the chosen anatomic target. Also, at that stage, only small numbers of patients with short follow up had been considered in published studies. An earlier report on thalamotomy using a GK had reported a 20% failure rate, with complete elimination of tremor in only 32% [248].

Four studies on use of SRS for Parkinson's Disease were identified and are summarised in Table 12. One of these was a prospective comparative study with radiofrequency posteroventral pallidotomy, which appears to be of good quality. Treatment outcomes were equivalent for the mean follow up of 20.6 months, though there is a latency associated with the SRS treatment of at least 2-3 months.

With SRS in treatment of tremor associated with Parkinson's, only case series were located. The large series from Los Angeles and Seattle include follow up of over 4 years, with the authors concluding on the basis of several studies reported in the literature that it is as effective as RF thalamotomy or deep brain stimulation but safer than either of those techniques.

A more cautious perspective on the safety of SRS in treatment of Parkinson's Disease is taken in a report by Okun et al. [249] who describe eight patients refrerred over 8 months to a clinic at Emory University, Atlanta for major complications associated with SRS (GK) for this condition. They comment that their report follows a review by Lang [250] suggesting there is little reliable evidence that radiosurgery can safely be applied to patients with Parkinson's Disease. Okun et al. comment on the delay in both benefits and complications in SRS treatment and note that in the group referred to them there had been considerable spread to adjacent structures, as evidenced by neurological complications that had occurred. They also draw attention to possible problems of targeting with SRS (though Young et al. [251] suggest that the results from their series indicate that imaging guidance was satisfactory) and with lesion size.

While encouraging results have been reported by one centre, the place of SRS in the treatment of Parkinson's Disease does not appear to be established. Further, good quality, comparative studies are required together with detailed consideration of the benefits and limitations of this and other options for management of patients with Parkinson's Disease whose condition is refractory to drug treatment.

Table 12: Studies on SRS treatment of Parkinson's Disease

Authors, study design	Patients/ Condition	Intervention	Outcomes	Comments
Duma et al., 1998 [252] Case series, outcomes – neurologists' rating using UPDRS, subjective patient opinions. 7 patients also assessed using general PD function 03/91 – 12/96	34 patients with PD resistant to medication and inappropriate for surgery. Los Angeles, USA	GK (to control tremor, thalamotomy) 160 Gy in n=16, 120Gy I n=22	Median follow up 28 mo (6-58) Tremor eliminated in 24%, excellent result in 26%, good in 29%, mild in 10.5%, no response in 10.5% Abstract mentions this approach less effective then other stereotactic approaches, though no comparison is given. Improvement by 1,2 or 3 UPDRS grades classified as mild, good, excellent	Apparently no recurrence of tremor during follow up period, though this is not mentioned. Authors consider this approach offers option for tremor control in patients unsuited to surgery.
Ohye et al., 2000 [253] Case series, from 9/93	N=31 N=22 PD, 5 essential tremor, 2 intention tremor Takasaki, Japan	GK	In most of 15 patients with >2y follow up, reduction in tremor started about 1y after irradiation and then progressed rapidly. In 5 patients, tremor had not sudbsided adequately by 1-1.5y post irradiation, 4 of these had second SRS – 1 improved (intention tremor), 2 needed surgery	Graphical presentation of changes in tremor over time for 15 cases. Approach to measurement of tremor not described. Non-PD cases not clearly distinguished
Young et al., 1998 [254] Non randomised comparative study 8/93 – 2/97	N=51 with refractory PD Seattle , USA	GK, n= 29, 34 treatments RF, n=22, 25 treatments Pallidotomy	Mean follow up 20.6 mo (6-48 mo) SRS group: 87% complete or near complete relief of dyskinesias, 7% improved. RF group: 83% complete or near complete relief of dyskinesias, 8% improved 66% of GK and 64% RF significant improvements in bradykinesia and rigidity No SS differences in UPDRS scores for two groups	Blinded pre and post treatment UPDRS score determination. Treatment selected by patient after informed consent discussion. Further details of the SRS treated group given in separate paper [251] Details of time course of response to treatment not given
Young et al., 2000 [255] Case series	N=102 with PD, 52 with essential tremor Los Angeles and Seattle, USA	GK for thalamotomy	Mean follow up 52.5 mo (11-93) for PD group At 12 and 48 mo 76.5% and 79.7% tremor free, 2.75 and 9.5% almost tremor free, 10.8% and 10.8% treatment failure SS and sustained improvements in UPDRS scores. Mean follow up for essential tremor group 29 mo. At 12 and 48 mo 78% and 71% tremor free, 14% and 18% almost tremor free, 8% and 6% treatment failure. Two minor, possibly permanent complications	

Epilepsy

Earlier experience with SRS of AVMs had indicated that epilepsy associated with such lesions frequently improved following treatment. Several of the studies located for the present assessment refer to the effect of SRS on seizures associated with the presence of an AVM, and are listed in Table 5.

There appears to be little in the literature concerning studies on use of SRS for other types of epilepsy. Schröttner et al., in a report from the group at Graz, describe use of a GK to treat 24 patients with medically intractable epilepsy associated with a tumour [256]. In most cases the tumour was a low grade astrocytoma. Patients were treated using a protocol that irradiated relatively large volumes of brain outside the tumour volume. With a mean follow up of 2.3y (1 - 4.4), overall 54% of patients became seizure free or had rare seizures, and there was worthwhile improvement in a further 17%. There was a higher rate of excellent results (66%) in 12 patients who received radiation over a larger volume of brain. Results were also better for temporal tumours and for cases where epilepsy had been experienced for 2.5y or less.

Regis et al. [257] report follow up of more than 24 mo on a group of 16 patients with drug resistant mesial temporal lobe epilepsy. In this group, 13 were seizure free and two were improved. Mean latency for seizure cessation was 12.8 mo. As pointed out by the authors, this form of epilepsy has a good outcome following limited temporal lobe resection.

The efficacy of SRS in the treatment of epilepsy appears not to have been established and use of this approach other than in association with treatment for AVMs or brain tumours should be regarded as experimental.

Non head and neck applications

Preliminary reports are beginning to appear on the use of newer LINAC -based approaches to treatment of conditions located outside the head and neck. A note from Takacs et al. (Los Angeles) [258] describes early experience in using spinal LINAC SRS for 19 patients with 26 metastases in the spinal column. Median follow up was 207 d. Of 23 lesions available for follow up, 10 decreased, 10 were stable and there were three treatment failures. There were five minor complications. Median charges for SRS were $17,095 (1 day hospital stay) compared with $39, 588 (10 hospital days) for spinal open surgery.

Ryu et al. (Stanford) [259] reported on the use of the CyberKnife for fractionated SRS in treating spinal lesions. Preliminary results are presented for 16 patients with AVMs, tumours and metastatic disease. Follow up ranged from 3 – 48 mo. No treatment – related side effects had been reported. Early follow up results indicated local control in 6 patients with tumours.

A paper by Uematsu et al. [260] reported use of a CT – guided frameless FSRT system to treat 50 patients with NSCLC, 21 of whom were considered inoperable. At a median follow up of 36 mo, 30 were reported to be alive and disease free. There had been no local progression in 94%. Three year survival rates were 66% overall and 86% in the operable cases.

COST AND ECONOMIC ISSUES

Table 13 summarises recent cost and economic studies on SRS treatments. The results from several reflect local situations and are not necessarily generalisable. That by Porter et al. has been referred to previously in the section on AVMs. Two of the studies indicate that a modified LINAC approach is the least costly option for small caseloads, with a dedicated SRS having the advantage for higher patient numbers. The Australian analysis by MSAC suggests a cost advantage to LINAC over GK over a range of scenarios.

A further comparison of interest is provided by Maguire et al. [214] who report that the professional charges at Duke University Medical Center are about $US17,000 for a course of FSRT compared to about $US25,000 for LINAC SRS.

As suggested by the HTA report from ANAES [17] there is a still a need for good quality economic studies and this is hampered by the limited data on clinical effectiveness of SRS. Longer term consequences of SRS treatment need to be considered in economic terms. There will also be a need to consider the costs and economic impact of newer options for SRS, such as the CyberKnife, in relation to GK and LINAC approaches.

Table 13: Cost and economic studies on radiosurgery

Study	Approach and condition	Centre	Type of analysis	Results	Comments
Becker et al., 1998 [261]	Modified and dedicated LINAC, GK	Tubingen, Germany	Cost comparison	Annual cost modified LINAC 137,000 DM, dedicated LINAC 787,500 DM, GK 1,118,500 DM	Abstract only; noted in MSAC report
Königsmaier et al., 1998 [262]	GK, modified and dedicated LINAC	Graz, Austria	Cost accounting approach, including capital, operating and staff costs	Modified LINAC 6,345 DM/patient at <175 per year. For >200/y, dedicated SRS is cheaper. At n=200, 6,561 DM for GK, 6,862 DM for dedicated LINAC	Estimates appear to make over-generous provision for staffing costs. No justification for assumption of higher downtime for LINAC Modified LINAC estimates for >175 not given
Manning et al., 2000 [162]	HSRT treatment of brain metastases	Richmond, USA	Departmental billing information	Median absolute cost of SRS $4,119 higher than HSRT	Actual costs of treatment not specified. Type of SRS not identified
Mehta et al.,1997 [263]	WBRT v surgery+WBRT v LINAC + WBRT Single brain metastasis	Madison, USA	Cost-effectiveness and cost utility estimates. Survival and outcomes data from literature, costs based on billing data	Incremental C/E ratio SRS + WBRT/ WBRT=$US 12,289 per LYS Incremental cost – utility ratio SRS + WBRT/ WBRT $US 10,573 per QALY	Reliance on data from Auchter, Patchell and Noordijk studies, with limitations that implies. QALY values based on time over which a KPS >= 70 was maintained.
Medicare Services Advisory Committee, 2000 [18]	GK and LINAC	Canberra, Australia	GK costs from submission made for coverage decision; LINAC costs from administra-tive data at an Australian centre	Cost ratio of GK equipment cost per treatment to LINAC equipment costs per treatment ranged from 1.7 –2.9 over a range of scenarios. At 200 treatments/y cost for the GK was $AUS 4,188 and cost for LINAC $AUS 2,499 - $AUS 1,614 the latter corresponding to a modified LINAC approach	Report notes some questionable assumptions in application, eg quality assurance costs for GK assumed to be zero and assumed 7 year interval for change of cobalt elements.
Ott, 1996 [264]	GK and craniotomy	San Diego, USA	Billing charges compared with nominal GK charge	For GK – eligible patients craniotomy charge $25,149 v $22,000 for GK charge	GK estimate makes no provision for follow up care
Porter et al., 1997 [64]	LINAC v surgery for small AVMs	Toronto, Canada	Cost – utility analysis	Benefit of 0.98 QALY from surgery at additional $CAN 6,937/case, incremental cost –utility ratio $CAN 7,100 for surgically treated patients	

OPTIONS AND REQUIREMENTS FOR ALBERTA

The previous assessments from AHFMR summarised some of the issues related to SRS that Alberta faces. Caseload for the province would be modest, with consequences for the cost effective operation of a dedicated SRS centre. Referral of patients out of province, particularly to centres in the USA, is expensive and there is continued uncertainty regarding the comparative merits of the GK and LINAC options for SRS and of SRS in comparison with microsurgery and other alternatives.

Referral outside the province continues to be costly. Advice from Alberta Health and Wellness is that for the period April 2000 – September 2001 there were 18 referrals of Alberta patients outside the country for SRS treatment, all but one of these at centres using the GK. There were seven referrals each of patients with acoustic neuroma and brain metastases and one each of persons with arteriovenous fistula, astrocytoma, trigeminal neuralgia and obsessive-compulsive disorder. Two of the treatments took place in Germany, the remainder in the US. Average charges for four acoustic neuroma cases treated in the US were $36,000 and for two treated in Germany $10,500. Average charges for treatment of five patients with brain metastases was $30,000.

The 1998 AHFMR report mentioned that the charge per GK procedure in the U.S. was estimated at $28,000 to $30,000 per patient. Estimated costs of different treatment options from the 1998 report are shown in Table 14 and included those for a projected LINAC facility in the province, which was not then in place.

Table 14: Summary of SRS and surgery costs for Alberta, 1998

Treatment modality	Cost
LINAC SRS Alberta	$ 4,000
LINAC SRS Ontario	$ 8,000 - $11,000
Microsurgery	$ 9,500
GK SRS United States	$ 29,500

Source: Schneider & Hailey, 1998 [1]

The 1998 report suggested possible caseloads for patients in Alberta with AVM, acoustic neuroma or brain metastasis who might benefit from SRS. There were an estimated 20-30 new cases of AVMs per year and 20-30 new cases of acoustic neuroma. Only a proportion of patients with these conditions would be candidates for SRS. The range for AVMs seems generally consistent with estimates made by Hillman on the basis of data over 11 years from a population in Sweden. Annual numbers of procedures per million population were 6 – 10 for microsurgery and 2 – 7 for radiosurgery and/or embolisation [265].

Since publication of the earlier AHFMR assessments an adapted LINAC – based SRS facility has been established in Calgary at the Tom Baker Cancer Centre, with the first patient being treated in February 2000. At present, the machine is used only for treatment of malignant tumours.

Any further development of SRS services in the province should take account of recent technical developments and organisational issues on the provision of radiosurgery treatment within Alberta. Discussion of such matters is outside the scope of the present report.

When referral with other types of conditions for SRS treatment out of province is being considered, an essential requirement should be that the patient is treated at a centre with considerable experience in management of the condition in question, both by SRS and by other means. There is no convincing evidence to support either the GK or the LINAC versions of SRS as being the technology of choice.

Consideration for referral should take account of the continuing poor quality of evidence of comparative benefit and of complications in all applications of SRS.

Additional options are becoming available through the wider application of FSRT and the introduction of non-cranial SRS (the CyberKnife) at some centres. These may become significant for treatment of a number of conditions.

DISCUSSION

The 1998 report from AHFMR found that there were limitations in the scope and quality of the studies that have been undertaken on SRS. "Notable features are the absence of comparative studies of the GK and LINAC approaches, and the still limited evidence from good quality trials of the effectiveness of either method" [1].

There has been little improvement in this situation. Evidence on the efficacy, effectiveness and economic impact of SRS remains very limited, with a notable lack of credible studies. Those that use and support SRS have not been good at comparing the clinical benefits and complications of this approach with those of other technologies.

It was proclaimed last year that more than 100,000 patients treated with SRS since the technique was first described in 1951 [14], but it is striking that this level of activity has occurred without strong evidence on benefits and risks. Some of the conditions and clinical situations for which SRS has been used do present challenges for assessment. Also, several of the major SRS centres have usefully documented their experience over many years. Nevertheless, as noted by every HTA report yet prepared, there are no studies that clearly establish the efficacy or effectiveness of SRS relative to other options in any application (other than use of WBRT alone for brain metastasis) or of different forms of SRS relative to each other. This is a dismal record.

SRS has an accepted place in the treatment of a number of conditions as an option where microsurgery is not possible and as an adjunct to surgical and other approaches. A number of commentators, including users of both LINAC and GK versions of SRS, have noted the need for a multidisciplinary approach, with the technology being seen as complementary to other treatments, notably microsurgery. This should be a key to any choices for referral of patients from Alberta. Either LINAC or GK SRS appear to be acceptable choices if SRS is to be used.

New options in this area, including the CyberKnife and wider use of FSRT, show promise and are likely to be of increasing significance. However, as with SRS, convincing evidence of their efficacy and cost effectiveness will be required.

As suggested in the 1998 AHFMR report, decisions on whether to refer individual patients for SRS will continue to require careful consideration of history and diagnostic findings by the specialists concerned and of the information on SRS efficacy in each application, as suggested by this and other assessments.

APPENDICES

APPENDIX A: METHODOLOGY

Search Strategy

Databases Searched	Subject headings (Bolded) and Textwords combinations
PubMed (Limited search to 1997 - January 24, 2002)	radiosurgery OR "stereotactic radiosurgery" OR "gamma knife" OR (linac OR linear accelerator* OR particle accelerators) AND (stereotactic OR stereotaxic) the above terms AND publication type: clinical trial (limited to human studies) OR publication type: meta-analysis (limited to human studies) OR publication type: practice guideline (limited to human studies) OR publication type: randomized controlled trial (limited to human studies) OR publication type: review (limited to human studies) OR in process records OR publisher supplied records OR case report OR comparative study OR economics OR costs and cost analysis OR treatment outcome OR outcome and process assessment (health care) OR Canada =1070 references OR radiosurgery OR "stereotactic radiosurgery" OR "gamma knife" (limited to human studies) AND case-control studies =231 references

EMBASE (Ovid) (1997-September 2001) Limited to human studies	exp *radiosurgery/ or (gamma knife or linac or linear accelerator or particle accelerator).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] and stereotactic.mp. and exp clinical trial/ or exp randomized controlled trial/ or exp major clinical study/ or exp meta analysis/ or exp practice guideline/ or exp case control study/ or exp case report/ or exp comparative study/ or exp review/ or exp economics/ or exp cost/ or exp cost benefit analysis or exp cost effectiveness analysis/ or exp cost utility analysis/ or exp health care cost/ or exp treatment outcome/ or exp Canada/ =406 references
CINAHL (Ovid) (1997-November 2001) Limited to human studies	exp *radiosurgery/ or (gamma knife or linac or linear accelerator or particle accelerator).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] and stereotactic.mp. and exp clinical trial/ or exp randomized controlled trial/ or exp major clinical study/ or exp meta analysis/ or exp practice guideline/ or exp case control study/ or exp case report/ or exp comparative study/ or exp review/ or exp economics/ or exp cost/ or exp cost benefit analysis or exp cost effectiveness analysis/ or exp cost utility analysis/ or exp health care cost/ or exp treatment outcome/ or exp Canada/ =7 references
PsycINFO (Ovid) (1997-November 2001)	exp *radiosurgery/ or (gamma knife or linac or linear accelerator or particle accelerator).mp. =3 references
EBM Reviews – ACP Journal Club (Ovid) (1991-March/April 2001)	gamma knife.mp or stereotactic radiosurgery.mp. or radiosurgery.mp. =0 references
Web of Science (Science Citation Index and Social Science Citation Index) (1997-2002)	(gamma knife OR stereotactic radiosurgery) AND (trial? OR comparative OR comparison OR meta analysis OR outcome? OR cost? OR economic? OR control*) =379 references
The Cochrane Library (Issue 4, 2001)	stereotactic radiosurgery or gamma knife =2 protocols, 3 DARE references, 23 controlled clinical trials, 19 HTA Database references and 6 NHS EED references
The Cochrane Library (Issue 1, 2002)	gamma knife =3 protocols (nothing else new from first search)
Other sources	The web sites of other HTA agencies (per the CCOHTA checklist) were also checked individually.

Using the search a total of 1,390 abstracts were identified.

From these, 332 publications were obtained for further inspection (nine were referred to only on the basis of abstracts). Seventeen of these had been previously considered in the earlier AHFMR reports.

Abstract selection and data abstraction were undertaken by the author.

Inclusion criteria

Papers were considered for inclusion if they reported outcomes of stereotactic radiosurgery treatments on humans, or alternative approaches to management of the same conditions that were being treated with radiosurgery. No restriction was placed on study design, but consideration of SRS case series was limited to those with patient numbers of 20 or more. There were no language restrictions. All reports that provided details of cost or economic studies were included.

Also considered were previous health technology assessments and systematic or good quality narrative reviews dealing with the use of stereotactic radiosurgery.

Exclusion criteria

Excluded from consideration were clinical case series using SRS with fewer than 20 patients; technical descriptions of apparatus, dose calculations; procedural descriptions; imaging and treatment planning approaches.

Data extraction

Clinical studies

1. Details of the article: authors, journal, year, language of publication and sources of funding;
2. study design: study type, number of centres, period of study , comparators used
3. study size: numbers of patients selected, treated and followed up
4. condition being treated: severity/ stage of condition
5. interventions: type of radiosurgery; other treatment technologies;
6. outcomes: nature, how measured, time of follow up, numbers followed up

Cost studies

Details of the article: authors, journal, year, language of publication and sources of funding

Type of study

Condition or conditions being treated

Type of intervention

Setting

Comparator

Basis of cost and other data

Discounting, sensitivity analysis

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